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JANUARY, 1917.

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STUDIES IN PELLAGRA:

I. TISSUE ALTERATION IN MALNUTRITION AND PELLAGRA

BY

JOHN SUNDWALL

II. CULTIVATION EXPERIMENTS WITH THE BLOOD AND SPINAL FLUID OF PELLAGRINS

BY

EDWARD FRANCIS

III. FURTHER ATTEMPTS TO TRANSMIT PELLAGRA TO MONKEYS

BY

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I. TISSUE ALTERATION IN MALNUTRITION AND PELLAGRA.[1]

By JOHN SUNDWALL, *Assistant Surgeon.*

While at the United States Public Health Hospital at Savannah it was my privilege to examine numerous tissues that had been obtained at necropsies of pellagrins. Effort was made to determine by special fixations and differential microchemical staining whether in pellagra any cellular changes or organisms are present which could be considered as characteristic of the disease. While these observations were not so extensive perhaps as they might have been, sufficient examinations were made to warrant certain conclusions. These are discussed under appropriate headings.

Later it was the writer's opportunity to examine numerous tissues which had been obtained at autopsies of certain animals which Prof. Carl Voegtlin had had under observation. These animals had been fed various diets by him with a view of producing, if possible, symptoms and tissue changes which are found in pellagra. In most instances the animals died in varying stages of emaciation. Lists of these diets, together with the clinical histories and autopsy findings, obtained from Prof. Voegtlin's notes, are included in this report.

There was a striking similarity of cell alterations seen in these animals and in those previously observed in the tissues procured from pellagrins. In fact, practically all the changes noted in the latter were observed in these animals.[2]

With a view of comparing these changes there are included in this report the morbid changes noted in the tissues of both series—pellagrins and experimental animals. The changes observed in the latter series are reported first, after which the alterations found in pellagrous tissue are considered.

PART I.—TISSUE ALTERATIONS IN ANIMALS RESULTING FROM VARIOUS VEGETABLE DIETS.

In most instances the tissues were procured immediately after the death of the animals. They were preserved in various fixation fluids, depending upon the particular structures to be preserved. The series consisted of monkeys, rats, pigs, and rabbits. The following is a summary of the findings:

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[1] Manuscript submitted for publication Aug. 20, 1915.

[2] The great resemblance of the chemical changes in the central nervous system of these experimental animals with those observed in pellagra were described by M. L. Koch and Carl Voegtlin in Hygienic Laboratory Bulletin No. 103.

I. MONKEYS.—VARIOUS DIETS DEFICIENT IN ESSENTIAL CONSTITUENTS.

MONKEY I.

Monkey fed on corn-oil cake. Began feeding May 13; progressive loss of weight from 3,675 grams to 2,150 grams at time of death, June 6.

AUTOPSY FINDINGS.

Very emaciated body; brain and cord removed and vertical sections taken of cerebrum near optic nerve—one in each hemisphere. Two sections of cord near first lumbar region also taken. Lungs normal; liver normal—53 grams—spleen dark; pancreas hemorrhagic; kidneys pale; adrenals normal; stomach, mucosa has small hemorrhages; small intestines, walls thin, hemorrhagic; colon shows profuse hemorrhages; entire gastro-intestinal tract empty.

MICROSCOPIC APPEARANCES.

Heart.—Myocardium: The muscle fibers are granular in appearance, cloudy swelling—much pigment in evidence but this pigment is not the typical pigment of brown atrophy—it is more or less diffuse throughout the cell, and in many instances it is difficult to distinguish it from the granular cytoplasm. The transverse striations are indistinct, many blood cells are seen beween the fibers—a mild degree of congestion.

Lungs.—This particular section shows much congestion of the alveolar capillaries, and the alveolar walls are thickened; much greenish brown pigment is also seen in these thickened walls and around the larger vessels and bronchi; no leucocytic infiltrations are observed. Small areas of lymphoid cells are seen near the bronchi in some instances; but these can not be considered as abnormal.

Liver.—For the most part this appears normal; slight congestion is seen in both the central and portal veins; many blood cells are also observed in the intercellular capillaries; the cytoplasm of the cord cells appears somewhat cloudy and not distinct as in the normal; the nuclei are vesicular; one very small focus of polymorphonuclear leucocytes is observed.

Spleen.—This organ shows pronounced pathological changes. The capsule is thickened; the entire spleen pulp is congested and hemorrhagic—in fact, the red blood cells practically obscure the pulp cells—the larger vessels are intensely congested; all the malpighian areas are undergoing amyloidosis; in some practically all the lymphoid cells are masked by amyloid which stains violet red in gentian violet; Van Gieson's stain shows hyalin changes in many of the central arteries. (See Fig. 3.)

Kidney.—The capsule is congested and torn away from the parenchyma; the stellate veins are also congested; the glomeruli for the most part are congested; the cells of the urinary tubules, especially convoluted tubules, are swollen; the cytoplasm is granular; a granular detritis fills many of these tubules, which stains red in eosin; the intertubular vessels in many instances are slightly congested. Sections from other portions of kidneys show great dilatation of both the collecting and urinary tubules.

Suprarenal.—Very few changes are observed in this organ. The cytoplasm is more reticulated than normal, especially in the zona fasiculata. This may indicate an increase of lipoids.

Lymph gland.—Capillaries and sinuses are intensely congested and contain much brown pigment.

Stomach.—Pyloric region: Epithelium, intact and normal throughout; the mucosa is congested, especially in that region surrounding the fundi of glands. The muscularis mucosae is not well differentiated from the submucosa; the latter, in certain places, is somewhat congested, the muscular layer appears normal; no parietal cells are seen.

Small intestine—upper part, jejunum.—Surface epithelium is broken; the mucosa is congested and hemorrhagic; in many instances these hemorrhagic areas come in contact with the lumen; no leucocytic infiltration is observed in the mucosa; the mucosa in this section has become separated from the muscularis mucosae; the latter appears normal; the submucosa is torn and broken, some of its vessels are congested, and in certain areas red blood cells are seen loose in the surrounding tissue; the muscular layer appears normal.

Small intestine—ileam.—The surface epithelium is broken, especially on the ends of the villi. In these instances the connective tissue mucosa comes in contact with the lumen. The mucosa is injected and hemorrhagic, and there is also an increase of the cellular elements—chiefly small lymphoid cells, although both polymorphonuclear leucocytes and plasma cells are abundantly seen. The goblet cells stain deeply in muchaematein; the muscularis mucosae is distinct; the submucosa is loose and many of its vessels are congested; a pronounced atrophy has occurred in the muscular layer—both layers are not more than one-half the thickness of normal. In many of these sections such changes have occurred in the epithelium and villi that it was necessary to use differential stains in order to determine the true nature of the tissues. (See Fig. 4.)

Nervous system.—Sections from tissue removed from cerebrum near optic nerve were prepared by the Pal-Weigert method and counterstained in lithium carmin. No abnormalities are observed in the cells of the cortex, and no degenerations are seen in the fibres leading from the cortex; the pia appears normal.

The spinal cord: Cervical region shows degeneration of the column of Burdach in the posterior tract. (See Fig. 1.) Lower dorsal region shows a diffuse degeneration of the myelin sheaths chiefly on one side. (See Fig. 2.) The degeneration is not limited to any particular tract, but occurs in the following regions: Anterior pyramidal, anterior and lateral margins of the anterior and lateral tracts, and a diffuse, ill-defined area in the posterior tract in both Gall's and Burdach's columns. As stated, these degenerated fibers are not sharply demarcated from the normal. The section gives the appearance macroscopically of a diffuse light band surrounding a darker zone of more normal fibers. The vessels in the gray matter are congested; some cells in the anterior horn are large and pale, although complete chromatolysis has not taken place; the other cells of the gray matter for the most part appear normal.

SUMMARY—POSITIVE FINDINGS.

Gross findings.—Very emaciated body; spleen, dark, congested; pancreas, hemorrhagic; kidneys, pale; stomach, small intestines and large intestines, hemorrhagic; small intestinal wall, thin and atrophic.

Microscopic findings.—Heart muscle, granular and pigmented; lungs, congested and pigmented; liver, slightly congested; spleen, intensely congested and has undergone amyloidosis; kidney, congested and a mild degree of albuminous degeneration; the lower intestinal tract, hemorrhagic, congested, and atrophic; spinal cord, degenerative changes in all tracts with pronounced changes in column of Burdach in cervical region.

MONKEY II.

Began feeding with corn-oil cake in various amounts March 14. The monkey, which at first weighed 3,100 grams, began to lose weight and weighed 2,085 grams at the time of death, May 21. Diarrhea; loss of weight, erythema on face, especially when exposed to the sun; coughing; and progressive weakness are some of the symptoms noted by Prof. Voegtlin.

AUTOPSY FINDINGS.

Body emaciated; central nervous system normal; liver pale; kidneys pale; spleen slightly hemorrhagic; intestines slightly hemorrhagic.

MICROSCOPIC APPEARANCES.

Heart.—Myocardium muscle fibers are much separated; in many areas the transverse striations are not so distinct as normal; no pigmentation is observed, nor is the sarcoplasm granular; a slight degree of congestion is present in both the larger vessels and the intermuscular capillaries.

Lungs.—The aveolar walls are markedly congested, and in some aveoli there are indications that hemorrhages have occurred; the larger vessels are congested, and the surrounding lymphatics contain much blackish pigment—probably foreign carbon.

Liver.—Marked changes have occurred. It is only after some study that one is convinced that the section is taken from the liver. Both the portal and central veins are congested, and in the former large cells (phagocytes?) are seen filled with dark-brown pigment; the intralobular capillaries are congested. The pronounced changes are seen in the liver cells; the typical cords are not seen, but the cells lie scattered without definite arrangement; some are atrophic, others are large; all forms are seen—some angular, others round or oval, and still others irregular in outline. The cytoplasm of many cells is vacuolated. These vacuoles vary in size and number for each cell, in many instances they are larger than the nuclei. They are found in cells near the central vein as well as in the peripheral portions of the lobules. The larger vacuoles are not the typical vacuoles of fatty degeneration and infiltration but suggest hydrops. In many cells the cytoplasm is granular. In many instances the cells normally present surrounding the central veins have disappeared; only a few remain. This section shows pronounced nutritional disturbances. No evidence of infection is observed. (See Fig. 5.)

The description above does not apply to all portions of the liver, as sections were examined where the cells and cords are more normal in appearance, and the disturbances are not so pronounced.

Spleen.—Capsule is thickened; a marked congestion of the spleen pulp is seen; no abnormal accumulation of polymorphonuclears is seen in the pulp; the red blood cells completely surround and break up the pulp cords so that the latter appear as small irregular islets in the red blood cells; the lymphoid tissue surrounding the arteries—Malpighian areas—are reduced in amount. There is also seen a beginning amyloidosis in these areas; however, they react only faintly to methyl violet.

Kidney.—Capsule appears normal; glomeruli for the most part are congested; cells of proximal convoluted tubules are slightly granular, the nuclei stain normally, the distal ends of these cells are broken and a granular detritis is found in the lumina; this is also true of the epithelial elements of the urinary tubules; the collecting tubules are similar in appearance to the urinary tubules; the interstitial vessels are congested.

Stomach—Fundus.—Superficial epithelium is eroded; this is also true of the cells deeper down in the glands where they are either completely or partially destroyed; the parietal cells stand out very plainly and appear normal, they appear to have resisted the degenerative changes; a slight increase of the cellular elements—round cells and plasma cells—is seen in the mucosa; the muscularis mucosae is normal; the submucosa is slightly congested; marked atrophy of the muscular wall has occurred.

Small intestine—Ileum (?).—Superficial epithelium is eroded; the naked villi project into the lumen, many of which are congested and hemorrhagic; numerous large plasma cells are seen in these naked and eroded villi; in many instances the villi are completely destroyed, ulcers. The goblet cells stain deeply in muchaematein and are well preserved where the epithelium remains intact; the submucosa is atrophic and slightly congested; the muscular coat is very thin.

Colon.—Superficial epithelium is eroded; the goblet cells are well preserved; the interstitial cells of the mucosa are atrophic, a mild congestion is seen in certain areas, no hemorrhage; the submucosa is slightly congested.

Cerebrum.—A mild congestion of both cortex and pia is noted. No other section from nervous system was examined.

Skin.—From region of external canthus, no noticeable changes in various epithelial layers; the connective tissue fibers of dermis and subcutaneous portions are separated—suggesting edema at one time—no congestion, no pigmentation.

SUMMARY.

Gross conditions.—Extreme emaciation; congestion and hemorrhage of gastrointestinal tract and nutritional disturbance in liver and kidney—both large and pale.

Microscopic anatomy.—Congestion of heart and lungs; marked disturbance of liver cells—atrophic, vacuolated, irregularly distributed; spleen extremely congested with beginning amyloidosis of the Malpighian bodies; kidney, slight congestion of all vessels and beginning albuminous degeneration; gastrointestinal tract congested and hemorrhagic.

MONKEY IV.

Fed cottonseed oil, raw eggs, and water, mixed in the form of cakes. Began feeding April 3; monkey then weighed 2,950 grams. There was a progressive loss of weight with a history of diarrhea, weakness. The monkey died July 17; weight 2,275 grams. The animal was paralyzed before death.

AUTOPSY FINDINGS.

Brain congested; cord normal; lungs, spleen, and liver congested; kidneys pale; stomach slightly hemorrhagic; small intestinal wall thin; large intestine slightly hemorrhagic and contains three worms resembling hookworms.

MICROSCOPIC APPEARANCES.

Heart.—This section shows fairly normal heart tissue; the transverse striations are plainly seen; all vessels, however, are filled with blood.

Lungs.—Intensely congested, both in the larger vessels and in capillaries of the alveolar walls; many of the alveoli are filled with œdematous masses; much foreign pigment is also observed in the perivascular lymphatic areas.

Liver.—Extremely congested; resembles nutmeg liver; the intralobular capillaries are so congested that in many areas the chains of liver cells are so broken that the cells have no regularity of position; the cytoplasm of many cells, especially at the periphery of the lobules, are granular, while those nearer the central veins have undergone pronounced cytoplasmic changes. (See Fig. 6.)

Spleen.—Extreme congestion; practically all the pulp area is taken up by red blood cells—only the nuclei of the pulp cells are seen; the Malpighian areas are reduced as a consequence of this extreme congestion; in many of these areas homogeneous masses are beginning to form which resemble amyloid; this, however, does not give a very positive reaction to methyl violet.

Pancreas.—Congested; apparent reduction in the number of islets, cytoplasm of pancreatic cells have undergone degenerative changes.

Kidney.—Congestion of all glomeruli; urinary and collecting tubules show slight disturbance of cytoplasm—granular and broken; all interstitial vessels are congested as well as the large arciform vessels.

Suprarenal.—Congestion, especially of the medulla and the zona reticularis; in certain areas hemorrhages are seen.

Small intestine.—Superficial erosion of epithelium; extreme congestion and hemorrhage of the mucosa; marked congestion of the submucosa; atony of the muscular layer.

Central nervous system.—Sections from the fissure of Rolando show congestion but no alterations in the pyramidal cells. Purkinje's cells in the cerebellum appear normal; many cells in the anterior horns of the dorsal spinal cord show chromatolysis; many are pale and swollen; pronounced congestion of this portion of the cord is also observed—both in the gray and white matter; the cells of spinal ganglia, in many instances, are large and pale; tissues prepared by Pal-Weigert's method show no degenerations in internal capsule, cerrebellum, medulla, or cord.

SUMMARY.

Gross conditions.—Emaciation; brain congested; lungs, liver, and spleen congested; stomach and large intestine slightly hemorrhagic; kidneys pale.

Microscopic findings.—Slight congestion of heart; congestion and edema of lungs; extreme congestion and albuminous degeneration of the liver; spleen extremely congested; congestion of kidney, pancreas, suprarenals, and small intestines—the latter extremely congested and hemorrhagic. The central nervous system shows slight alterations in the cells of the cord, both in the anterior horn cells and spinal ganglia, although no tract degenerations are seen.

MONKEY V.

Fed on yellow corn meal and sweet potatoes. Original weight at beginning of feeding, May 5, was 2,500 grams. At time of death, June 27, monkey weighed 1,865 grams. Loss of weight, diarrhea, and a final stupor from which the animal could not be roused mark the chief clinical observations.

AUTOPSY FINDINGS.

Same as monkey No. VII, which died first.

MICROSCOPIC APPEARANCES.

Heart.—Identically same condition as monkey No. VII.

Lungs.—Similar to that of monkey No. VII. Potassium ferrocyanide and hydrochloric acid show that the pigment is not hemosiderin.

Liver.—A mild degree of congestion which includes the central and portal veins and the intralobular capillaries; the congestion is not so intense as that seen in this organ in No. VII. Pigment is not hemosiderin.

Spleen.—Intense congestion and pigmentation with hyalin changes in the Malpighian areas—these are not so intense, however, as seen in No. VII.

Kidney.—This section is much similar to No. VII. The glomeruli are mildly congested; great destruction of the cytological elements of the urinary tubules—especially the convoluted tubules where the cytoplasm is granular, broken, or vacuolated, this condition is seen chiefly under the capsule; marked dilatation of many urinary tubules present a similar picture to the urinary tubules in No. VII so far as the cytoplasmic disturbances are concerned; a mild congestion of all vessels exists.

Stomach—fundus.—In some areas the superficial epithelium at the summits of the glands is eroded, in other areas it is normal; a mild congestion of the mucosa exists throughout; the submucosa is slightly congested; the muscular layer appears normal.

Intestines.—Most pronounced pathological changes are seen in this section. The entire mucosa, with the exception of the very bottoms of the glands, is composed of inflammatory tissue; the most superficial area is composed of necrotic masses and fibrin; below this is a zone of cellular elements—polymorphonuclear, plasma, endothelial, and red blood cells; this is a typical picture of an ulcer; the submucosa is intensely hemorrhagic, congested, and infiltrated with cells; the muscularis mucosæ is not seen; no line of demarcation exists between the mucosa and submucosa; the muscular layer is also congested. This section is so altered that with the ordinary stains it was impossible to determine from which part of the gastro-intestinal tract it had had origin; by use of muchaematein, goblet cells were seen in a very few glands at one end of the section; in all likelihood this was taken from the jejunum. (See Fig. 7.)

SUMMARY.

Gross findings.—Similar to Monkey VII; emaciation; congestion of liver and spleen; congestion and hemorrhage of the gastro-intestinal tract.

Microscopic findings.—Degeneration of myocardium; congestion of liver; spleen congested and hyalin changes; kidney cytoplasmic disturbances, degeneration of urinary and collecting tubules; stomach superficial erosions; ulceration, hemorrhage, and congestion of the intestines.

No tissues from the central nervous system were examined.

MONKEY VI.

Fed on a diet of corn meal and sweet potatoes—50 grams of each daily. Began feeding May 5; weight of monkey was then 2,300 grams. The loss of weight was progressive, and on June 3 it weighed 1,580 grams. It died July 5.

AUTOPSY FINDINGS.

Membranes of brain injected; cortex of brain congested and slightly injected; cord normal; kidneys pale; adrenals normal; spleen hemorrhagic; pancreas normal; liver normal; heart pale, firm, systolic; lungs contain patches of black pigment; large intestine hemorrhagic, contains large number of worms.

MICROSCOPIC APPEARANCES.

Heart.—Muscle fibers show some indistinctness of transverse striations; a congestion also occurs.

Lungs.—Extreme congestion of the capillaries of the alveolar walls; perivascular accumulations of round cells; the congestion and lymphoid cells occur only in certain areas; much black pigment is also seen in the perivascular and peribronchial lymphatics—appears to be foreign pigment.

Liver.—Congestion of all vessels including the intralobular capillaries; atrophy of the most centrally placed cells and albuminous degeneration of many cells; no fatty infiltration or pigmentation is seen.

Spleen.—Extreme congestion of all pulp areas; Malpighian bodies reduced in area owing to this congestion, beginning amyloid changes are observed in these bodies which react only faintly to methyl violet.

Pancreas.—Mildly congested; islets of Langerhans do not stand out clearly, nor are they as numerous as in the normal tissue; when seen they are not clearly differentiated from the surrounding pancreatic cells; this same condition has been observed in practically all pancreatic tissues taken from this series of monkeys.

Kidneys.—Capsule normal; glomeruli slightly congested; cytoplasmic disturbances of the cells of the urinary and collecting tubules; many of these cells are granular, others broken, vacuolated—hydrops; practically all interstitial capillaries are congested.

Stomach.—Practically entire mucosa either completely destroyed or substituted with inflammatory tissue; in some areas the fundi of the glands alone remain; in the latter, one sees extreme congestion and hemorrhage; the ulcerous areas possess the usual inflammatory cells; it was essential to use muchaematein to determine the nature of this section; the submucosa and muscular layer are intensely congested. (See Fig. 8.)

Intestines.—Sections from this portion of the gastro-intestinal tract show the same conditions as described above for the stomach.

Central nervous system.—Meninges congested; many pyramidal cells in the fissure of Rolando show slight degenerations—such as chromatolysis, paleness, and in some instances slight pigmentation; cells in the anterior horn of the spinal cord, especially in the dorsal region, likewise show retrograde changes, some pale, others vacuolated, others again have completely disappeared; all cells, however, do not show these changes; Pal-Weigert's method shows degenerated fibers in the internal capsule irregularly distributed; also degenerated fibers in all the tracts of the cord; in the cervical region, the extent of degeneration is so great in the column of Burdach that it appears well demarcated from the column of Goll. In the dorsal region, the degenerations have advanced more in the column of Goll, especially in the median line; this is also true in the lumbar enlargement.

SUMMARY.

Gross findings.—Membranes of cortex as well as cortex congested and slightly injected; heart pale and firm; black pigmentation of lungs; spleen hemorrhagic; large intestine hemorrhagic.

Microscopic findings.—Heart practically normal except for indistinctness of transverse striations; lungs extreme congestion; liver congested with cytoplasmic degenerations of liver cells; spleen extreme congestion; pancreas only mildly congested with indistinctness of islets and an apparent reduction in numbers; kidneys albuminous degeneration of urinary tubules and congestion throughout; stomach and intestines hemorrhagic, congested and ulcerated; central nervous system congestion of meninges; slight degree of degeneration of the pyramidal cells of cortex and the anterior horn cells of the cord; degenerations of fibers in the internal capsule and cord, in the latter especially in the column of Burdach in the cervical region and the column of Goll in the dorsal and lumbar region.

MONKEY VII.

Began feeding yellow corn meal, May 5, 1914. After a history of progressive loss of weight (original weight 2.270 grams), inanition, diarrhea, etc., it died June 28; weight 1,730 grams.

AUTOPSY FINDINGS.

Lungs normal; heart dilated; liver congested; stomach and intestines show hemorrhage; spleen congested; no signs of scurvy; very emaciated body; few worms in intestines; total weight of brain 78.5 grams; cord 3.505 grams.

MICROSCOPIC APPEARANCES.

Heart.—Myocarium—certain areas, especially those fibers near the endocardium, show vacuolization (hydrops) and numerous albuminous granules; the vacuoles surround the nuclei for the most part; the transverse striations are either faintly seen or absent in most of the myocardial fibers. All vessels including the myocardial capillaries are congested. (See Fig. 9.)

Lungs.—Few changes are seen; the alveolar walls are thickened; the peribronchial and perivascular connective tissue contain much brownish, yellowish pigment; this pigment is also seen here and there in the alveolar walls; where blood is present in the larger vessels pigment of the same color is seen either diffuse or in certain cells; only a part of the pigment gives the hemosiderin reaction with potassium ferrocyanide and hydrochloric acid. The largest amount is in all probability hemoglobin precipitated by the formalin used in fixation.

Liver.—This organ is intensely congested, both central veins and the portal veins; the blood contains very much pigment, but as these tissues were fixed in formalin perhaps no pathological significance can be attached to it; the liver capillaries are also congested and as a result the cord cells are thinned and separated from each other; the cords are distorted; the cells nearest to the central veins are most affected; many lobules give characteristic appearance of nutmeg liver.

Spleen.—Intensely congested; the pulp cells are masked by this congestion and the characteristic pigment is seen as described above, which is either within the endothelial leucocytes as granules or free; the spleen is atrophic, as more than the usual number of Malpighian areas are seen; in many of these hyalin changes have occurred in the central arteries; there is also an increase of the connective tissue elements throughout.

Kidney.—Capsule congested; glomeruli are either normal in appearance or slightly congested; the urinary tubules, especially the convoluted tubules, show disturblances of the cytoplasmic elements of the cells; in the cytoplasm are seen vacuoles or reticulations; the ends of the cells forming the lumina are broken and ragged, albuminous granules are also seen; the lūmina are wide, both from dilatation and as a consequence of the destruction of the proximal ends of the cells; the cells of the other constituents of both the urinary and collecting tubules show similar changes; considerable congestion is seen in all vessels, the blood of which contains much pigment-hemoglobin.

Suprarenals.—Congestion and hemorrhage are seen in both the medulla and cortex with the characteristic pigment; the medulla is atrophic.

Stomach—fundus.—Mucosa congested; parietal cells in many instances are broken and atrophic; this is also true of the other cells of the fundi of the glands; the mucosæ muscularis is normal; the submucosa is congested; the muscular layers appear normal.

Small intestine—ileum.—In many instances the villi are eroded, some are completely gone, others more than one-half of their lengths; the submucosa is greatly infiltrated with lymph, plasma, and endotholial cells, few leucocytes are also seen, these cell infiltrations come in contact with the lumen-ulcers, the vessels are congested; the muscular layer is atrophic, the fibers of the inner layer are broken and separated from each other.

Large intestine.—Mucosa much similar to that described for small intestine, more polymorpholeucocytes, however, are seen, and in some instances these form small foci; submucosa and muscular layer are normal.

Central nervous system.—A mild congestion of the meninges is seen; this is also true of the cerebral cortex; no changes are observed in the pyramidal cells except that spaces are seen between many cells and the surrounding neuroglia—this, however, may be due to the fixative; Pal-Weigert's method shows little or no degeneration of nerve tracts from this section of the cortex-frontal lobe. Spinal cord, dorsal region—a small area of degenerated fibers is observed macroscopically in the median line of the posterior tract; this area is included within the column of Goll; however, not all the fibers within this area are degenerated; many of the cells of the anterior horn appear swollen and pale, the Nissl's bodies being reduced; the central canal is dilated and filled with a granular detritis. (See Fig. 12.)

SUMMARY.

Gross findings.—Extreme emaciation; congestion of liver and spleen; congestion and hemorrhage of the gastro-intestinal tract.

Microscopic findings.—Degeneration of myocardium; liver extremely congested; spleen congested and hyalin changes; kidney mild degree of albuminous degeneration; suprarenals slightly congested; stomach congestion and erosion of epithelium; small and large intestines congestion of both mucosa and submucosa with erosion of villi, ulcers, atrophy of the muscular layer of the ileum especially; nervous system degeneration of fibers in the tract of Goll.

MONKEY VIII.

Began feeding monkey yellow corn meal on May 5; from then on it began to lose weight, became gradually emaciated and finally died, May 30, from marked inanition.

AUTOPSY FINDINGS.

Moderate increase of fluid in the subdural space; heart flabby; liver red and congested; kidneys pale; adrenals markedly red and congested; the gastro-intestinal tract hemorrhagic, especially was this true of the lower jejunum and colon.

MICROSCOPIC APPEARANCES.

Heart.—Ventricular wall marked congestion of all blood vessels; transverse striations are not so definite as seen in the normal; longitudinal striations are normal in appearance; Van Gieson's stain shows a general increase of collagenic fibers.

Liver.—Marked congestion of both the central and portal veins is seen; the chains of liver cords are broken up into irregular, interrupted chains, some even forming little islets of liver cells—this condition is chiefly due to congestion of capillaries; the cytoplasm of the liver cells is granular; the nuclei as a rule stain more faintly than normal; no pigmentation or fatty degeneration is seen.

Spleen.—The entire pulp is filled with red blood cells; Malpighian corpuscles are reduced in areas as a result of this intense congestion; this is a typical picture of passive congestion.

Pancreas.—Marked congestion of all blood vessels; many islets are very indistinct and difficult to make out from the surrounding acini, as no sharp line of demarcation exists between them. The acini also are congested.

Kidney.—The capsule is congested, loose, and in practically all the sections it is torn and separated from the cortex; the glomeruli as a rule are of normal size, many possess numerous red blood cells—showing a slight stage of congestion. The convoluted tubules are in many instances granular, some show hydrops wherein the entire cell is enlarged and vacuolated; the nuclei as a rule, with the exception of those in vacuolated cells, are normal in their staining reactions. The remaining elements of the renal and collecting tubules are apparently normal. The lumina of the latter in many instances contain a granular detritis. There is a general presence of red blood cells in all the vascular elements, indicating a slight degree of congestion.

Certain focal areas are seen wherein the cytoplasm is broken, stains faintly, and the nuclei fail to stain. These areas may include both glomeruli and tubules—areas of focal necrosis. The presence of these focal necrotic areas, mild congestion, and the granular condition of the proximal tubules indicate a toxic disturbance of the kidney.

Suprarenal.—The capsule is congested; marked congestion and hemorrhage is seen in the cortical substance, especially in the zona fasiculata; the cells of this zone are much more vacuolated than in the normal, showing an increase of lipoid substances; much pigment is seen in the terminal cells of the zona reticularis—this, however, can not be considered as abnormal in amount; the sinuses of the medullary portion are filled with red blood cells; no alterations appear in the chromaffin cells.

The marked lesions here are the hemorrhages and congestions seen in the zona fasiculata, the cytoplasm of these cells being very granular.

Stomach—pyloric region.—Slight congestion of the vessels of the mucosa is practically the only abnormality found. Some vessels in the submucosa and muscular layer are also congested. The epithelial cells are normal; Fundus region, same as pyloric.

Small intestine—ileum.—Epithelium on tips of villi eroded; remainder of epithelial cells of glands are normal; mucosa is congested and many polymorphonuclear leucocytes are seen, however not to such an extent as is seen in the section from the colon; the muscularis mucosae is intact throughout; the submocosa is atrophic and congested; atrophy and thining of the muscular wall is also observed.

Colon.—Superficial epithelium eroded; extreme congestion and hemorrhage of mucosa; in many instances red blood cells are seen in the lumina of the gland tubules; many polymorphonuclear leucocytes are also seen in the mucosa; these have a tendency to accumulate into foci which are in free contact with the lumen—ulcers; goblet cells stain only faintly in muchaematein.

Nervous system.—Small pieces from the following tissues were prepared for microscopic study by Pal-Weigert's method and the method for demonstrating Nissl bodies: Cerebrum, fissure of Rolando and internal capsule; cerebellum, vermis; cord, cervical and lumbar enlargement; vagus nerve; sympathetic trunk with ganglia; spinal ganglion. Consequently it was possible to study both the cells and axones with their myelin sheaths.

Pronounced changes are seen in the column of Burdach in the cervical enlargement, where practically all the myelin sheaths are in stage of degeneration; this degeneration is sharply demarcated from the column of Goll. Many cells in the spinal ganglia have undergone chromatolysis; there is also seen an increase of the pericellular connective tissue elements. (See Fig. 11.)

SUMMARY.

Gross findings.—Moderate increase of cerebrospinal fluid; heart flabby; liver congested; kidneys pale; adrenals markedly congested; gastrointestinal tract hemorrhagic, especially in lower part.

Microscopic findings.—Heart congested and muscles have undergone retrogressive changes; liver congested and cells have undergone pathologic changes; spleen intensely congested; pancreas congested; kidney slight congestion, disturbance of the cells of the proximal convoluted tubules, focal necrotic areas; suprarenals intensely congested and hemorrhagic; gastrointestinal tract congested, hemorrhagic, and atrophic, each increasing in degree as the lower end is approached; spinal cord degeneration of Burdach's column, chromatolysis of spinal ganglia cells.

MONKEY IX.

Fed on fresh carrots exclusively for five months and three weeks. During this time it lost considerable body weight and showed a persistent diarrhea after first weeks of the feeding.

AUTOPSY FINDINGS.

Extremely emaciated; skull and spine bones hard (not brittle); cord normal; brain normal; heart congested; no excessive fluid, right heart not dilated; lung normal; liver congested; spleen very small, congested; kidney congested; pancreas normal; abdominal lymph glands enlarged; stomach fundus extremely hemorrhagic; large intestine normal, contains a few worms resembling hookworms; duodenum slightly hemorrhagic; ileum slightly hemorrhagic; teeth not loose; no hemorrhages in skeletal muscles; no signs of scurvy; femur contains red marrow.

MICROSCOPIC APPEARANCES.

Heart.—Myocardium, muscle fibers are shrunken, no striations are seen, the sarcoplasm is granular and pigmented, the pigment, however, is not hemosiderin, the nuclei stain faintly but appear prominent owing to the atrophic cells; all vessels are congested.

Lungs.—Contain foci of lymphoid cell infiltrations but no true tubercles are seen; numerous areas of consolidation are also seen in which the alveolar walls can still be made out; the alveoli in these areas are filled with large round hyperplastic endothelial cells. Considerable carbon pigment is seen surrounding the bronchioli. The capillaries are intensely congested.

Liver.—Intensely congested. The chains of liver cells are broken as a result of this congestion. Many of the liver cells, especially those in close proximity to the central veins, are atrophic; others again are vacuolated, fatty changes.

Spleen.—The capsule and trabeculae are especially prominent, the Malpighian areas appearing as minute points. The pulp is extremely congested;

large endothelial cells are seen throughout this pulp which are filled with red blood cells and pigment; the latter reacts with potassium ferrocyanide and hydrochloric acid forming a deep blue color—hemosiderin.

Kidneys.—A mild congestion is observed, otherwise no pathological changes are seen.

Stomach.—The mucosa and submucosa in this section are congested. The epithelium of the proximal end of the gastric glands are atrophic and in some areas completely eroded. An increase in the connective tissue of the mucosa is noted. In this mucosa few parasitic eggs, granular, and oval in outline, are seen.

Small intestine—jejunum.—Intense congestion of both the mucosa and submucosa are present. In some areas the mucosa is completely gone and the muscularis mucosae is exposed.

Colon.—This structure is intensely congested throughout. Parasitic eggs similar to those in the stomach are seen in the mucosa.

Pancreas.—Slightly congested; many of the acini cells are vacuolated; the islet cells appear normal.

Cerebrum.—The cortex and pia are mildly congested; the former possess numerous vacuoles (edematous)—this latter condition was especially prominent in the formalin fixed tissue; in this tissue the pyramidal cells appeared somewhat shrunken and spaces are seen between them and the ground substance of the cortex. In tissue fixed in alcohol these cells appear somewhat swollen and chromatolysis has occurred. Many pyramidal cells show eccentric or peripheral nuclei. (See Fig. 13.)

Cerebellum.—The Purkinje's cells stain faintly; an interesting condition here is that these cells are completely embedded within the molecular layer.

Spinal cord.—Dorsal and lumbar region. As a rule the anterior motor horn-cells (alcohol fixation) show chromatolysis of Nissl's granules; many are slightly vacuolated (fatty degeneration). In formalin fixed tissue these cells appear shrunken, the nuclei, instead of being vesicular in form, stain deeply and solidly throughout; between the cells and surrounding matrix, spaces are seen. Evidences of degeneration of the tracts are present. This degeneration is more or less diffuse throughout the white matter. Unfortunately none of this tissue was prepared by the Pal-Weigert's method, consequently it was impossible to accurately determine the degree and extent of the degeneration; however, it is suggestive of the appearance of similar tissue in Monkey I. No degeneration was noted in the vagus or femoral nerves. (See Fig. 14.)

SUMMARY.

Gross conditions.—Extreme emaciation; heart congested; liver congested; spleen atrophic; kidney congested; abdominal lymph glands enlarged; stomach and small intestines hemorrhagic.

Microscopic anatomy.—Heart congested, loss of transverse striations, muscle cells atrophic and granular; lungs congested, alveoli filled with red blood cells and endothelial cells; liver intensely congested with broken cell chains, cells atrophic and vacuolated; spleen extremely congested and pigmented, hemosiderosis; stomach, small intestines, and colon are congested and ulcerated; central nervous system, chromatolysis of nerve cells and diffuse degeneration in tracts.

SUMMARY OF CELLULAR CHANGES FOUND IN MONKEYS.

Autopsy findings.—Various degrees of emaciation, from mild to extreme; heart pale, firm; lungs congested, pigmented; liver large, pale, congested; spleen dark, congested, atrophic; kidney large, pale; pancreas hemorrhagic; retroperitoneal lymph glands enlarged; gastrointestinal tract congested, hemorrhagic, ulcerated, muscular wall atrophic; brain congested; meninges congested; increase of cerebrospinal fluid.

Microscopic.—Heart loss of striations, albuminous degeneration, hydropic degeneration, atrophy of muscle cells; lungs mild to extreme congestion, œdematous, herzfehlerzellen; liver congested, cirrhosis, albuminous degeneration, fatty degeneration, hydropic degeneration, atrophy; spleen intensely congested, pigmented-hemosiderosis, amyloidosis, hyalin changes, proliferation of endothelial cells of pulp which contains congested red blood cells and pigment, reduction of Malpighian areas; pancreas congestion, indistinctness, and apparent disappearance of islets; kidney congestion, albuminous degeneration, focal necrosis; suprarenals slightly congested; gastrointestinal tract congestion of all layers, hemorrhagic, ulcerated, atrophic muscular walls, superficial erosions of epithelium; central nervous system, cerebrum, congestion of cortex; pyramidal cells chromatolysis, peripheral arrangement of nuclei, pigmentation; degeneration of fibers in internal capsule; spinal cord degeneration of Burdach's column in cervical region; dorsal region degeneration of Goll's column, diffuse degeneration in other tracts; anterior horn and spinal ganglial cells chromatolysis, swollen; meninges congested.

2. WHITE RATS, SERIES I.—CELLULAR CHANGES RESULTING FROM CORN-OIL CAKE DIETS.

The following statements regarding the diet, the subsequent effect of the diet, and the autopsy finding are summarized from Prof. Voegtlin's notes.

The diet in each instance was composed of various grades of corn-oil cake. In the majority of cases there was much loss of weight before the animals were finally necropsied. In some cases this loss was not progressive, but fluctuations occurred from day to day.

The tissues were obtained in a very fresh condition as the animals were chloroformed. Tissues were fixed in formalin.

RAT I. SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; spleen dark; liver congested; kidneys congested.

MICROSCOPIC APPEARANCES.

Lungs.—Alveolar walls, thickened and congested; some alveoli show edema; the walls possess much blackish and brownish-black pigment; the larger vessels are also congested; large areas of lymphoid cell infiltrations are seen.

Liver.—A mild degree of congestion is seen in both the central and portal veins; this congestion is also seen in many of the intralobular capillaries. No alterations, however, are noted in the liver cells. The cells contain much hemosiderin.

Kidneys.—Glomeruli are normal in appearance; the epithelium of the urinary tubules are as a rule normal, in certain areas, however, many tubules show broken and granular epithelial cells; the collecting tubules show no alterations; a mild degree of congestion is seen in many of the interstitial vessels.

Spleen.—The pulp areas are moderately congested throughout; the pulp cells as a rule are filled with brownish-black pigment granules; considerable atrophy of the pulp substance has occurred, and as a consequence the Malpighian areas appear larger and more numerous than normal. The pigment granules react with potassium ferrocyanide and hydrochloric acid and consequently are hemosiderin. (See Fig. 10.)

RAT II, SERIES I.

AUTOPSY FINDINGS.

Lungs normal; spleen normal; kidneys congested; liver congested.

MICROSCOPIC APPEARANCES.

Lungs.—Much thickening of the alveolar walls are noted; in many areas there is complete consolidation; the latter areas are made up of new connective tissue cells, round cells, and many cells which contain brownish black pigment; a mild degree of congestion exists throughout.

Liver.—A much more pronounced congestion is noted here than in this organ of Rat I; the congestion is especially marked in the intralobular capillaries; the liver cells show considerable alterations—chiefly a granular change has occurred in these cells, many are atrophic.

Spleen.—The section shows much alteration from the normal structure of the spleen; it is atrophic; the trabeculae are very prominent; the Malpighian areas do not stand out prominently, but are small and gradually fused with the pulp cells. Evidently there has been proliferation of the latter with a pronounced decrease of the lymph cells; numerous endothelial cells contain pigment granules.

Kidneys.—A mild granular condition of the urinary tubules, especially the convoluted tubules—otherwise the section does not show any alterations; a mild degree of congestion is observed, but not to such an extent as seen in this tissue in Rat I.

RAT III, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; spleen dark; kidneys congested; liver dark; intestines congested.

MICROSCOPIC APPEARANCES.

Lungs.—Thickened alveolar walls; pigmentation and congestion are the changes seen here; this section resembles a similar section taken from Rat I. The characteristic pigment is present which is composed of two kinds: (1) Pigment which reacts readily to potassium ferrocyanide and hydrochloric acid—hemosiderin and is intracellular; (2) pigment which is both intra and extracellular, chiefly the latter, and is in all likelihood precipitated hemoglobin as the tissue was fixed in formaline. Both pigments are seen in the same cells. A black pigment (carbon?) is also seen in many of the perivascular and peribronchial lymph spaces.

Liver.—This section resembles a similar section taken from Rat I; a mild degree of congestion anl cytoplasmic disturbances such as granules and vacuoles are the alterations observed.

Spleen.—This tissue is similar to that seen in Rat I; the congestion and pigmentation are the striking features.

Kidneys.—Many of the glomeruli are vacuolated—fatty infiltration; cytoplasm of urinary tubules, especially convoluted tubules, is much broken, granular, vacuolated, and reticulated—showing albuminous degeneration; this is also true for the collecting tubules; the arcuate vessels are filled with blood.

RAT IV, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; liver congested; small intestine congested; right kidney congested; left kidney substance transformed into large tumor, 2.5 cm. diameter.

MICROSCOPIC APPEARANCES.

Lungs.—Extreme congestion; alveolar walls thickened; many areas of total consolidation; extreme pigmentation throughout; large areas of lymph cell infiltration; alveoli have lost normal structure; majority appear round, as if they had contained fluid.

Liver.—Congestion of central and portal veins; the intralobular capillaries are also congested; liver cells show numerous albuminous granules; many are atrophic.

Spleen.—Very congested; pulp contains numerous pigmented cells, similar to Rat I; the Malpighian bodies are somewhat atrophic.

Kidneys.—Extremely congested; the usual albuminous degeneration is observed in the epithelium of the urinary tubules, especially the convoluted portions; many glomeruli are filled with red blood cells.

Tumor mass.—This occupied the position of the left kidney; it is composed chiefly of cells whose cytoplasm stains very faintly; the cytoplasm appears vacuolated or reticulated. In some areas these cells are grouped into islets of varying sizes, being surrounded by connective tissue. Vessels in these connective-tissue septa are congested. Congestion occurs throughout the tissue. This tumor resembles hypernephroma.

RAT V, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; liver congested; kidneys congested; spleen congested; intestines congested and contain bloody fluid.

MICROSCOPIC APPEARANCES.

Lungs.—Alveolar walls thickened and congested; the characteristic pigmentation is present in the endothelial cells; many alveoli are edematous, others enlarged and rounded as if previously filled with fluid; in fact, no normal alveoli are seen; areas of complete consolidation are also noted; areas of lymph cell infiltrations are present.

Liver.—A mild degree of congestion is noted in both the central and portal veins; the congestion in the intralobular capillaries is not so marked as in the sections already described; some liver cells are granular but not to such a degree as observed in other sections.

Spleen.—Pigmentation of the pulp cells is the most characteristic picture in this section. The pigment is intracellular and is composed of hemosidorin, as it reacts readily to potassium ferrocyanide and hydrochloric acid; other non-reacting pigments—within the endothelial pulp cells; although much congestion is present, it is not present to such an extreme degree as observed in similar tissue from other animals.

Kidneys.—Appear more normal than others examined—only a slight granulation is observed in cells of convoluted tubules. Accessory suprarenal gland tissue is observed near papilla.

RAT VI, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; liver congested; spleen congested; kidneys congested; small intestine congested.

MICROSCOPIC APPEARANCES.

Lungs.—Identically the same as seen in Rat V—congestion, consolidation, pigmentation, edema and thickened alveolar walls.

Liver.—Congestion of both central and portal veins; in many areas there is also seen marked congestion of the intralobular capillaries; a slight diffuse albuminous granular degeneration is also noted.

Spleen.—The typical pigmentation is observed in the pulp cells; an apparent hyperplasia of pulp cells has occurred; numerous blood cells are seen in this pulp; many vessels—central arteries in the Malpighian bodies—appear to have undergone hyaline changes.

Kidneys.—Only a mild degree of congestion is observed; in certain areas pigment is seen, but it is hemoglobin and not hemosiderin; the parenchyma shows a slight degree of cytoplasmic disintegration.

RAT VII, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; spleen dark; kidneys congested; small intestine congested.

MICROSCOPIC APPEARANCES.

Lungs.—Extreme thickening of alveolar walls; consolidated areas; much pigmentation; large areas of lymph cell infiltration surrounding some of the bronchii; extreme congestion.

Liver.—A moderate degree of congestion of the central and portal veins; also a slight congestion of capillaries. No alterations were observed in the liver cells.

Spleen.—Typical pigmentation.

Kidneys.—The usual picture of granular cytoplasm of the cells of the urinary tubules and a moderate degree of congestion is observed.

Intestines.—Entire mucosa and submucosa completely absent in certain areas of this section; the former layers occupied by fibrin; the latter extends to the muscular layer.

RAT VIII, SERIES I.

AUTOPSY FINDINGS.

Lungs hemorrhagic; liver dark; spleen dark; kidneys congested; small intestine congested.

MICROSCOPIC APPEARANCES.

Lungs.—Characteristic picture of thickened alveolar walls, with congestion and extreme pigmentation; alveoli enlarged and irregular in outline; the pigmentation is practically all precipitated hemoglobin.

Liver.—The typical congestion is present; the intralobular capillaries are much more congested here than in many of the other livers observed; the resultant atrophy and granulation of the liver cells, especially those in close proximity to the central veins, are observed; many cells are pigmented; sections treated with potassium ferrocyanide and hydrochloric acid show that the pigment is chiefly hemoglobin and not hemosiderin; in many cells, however, the latter is found; many liver cells appear diffuse blue after this treatment.

Kidneys.—Albuminous degeneration—broken epithelial cells, granular cells—are seen in the various urinary tubules; a mild degree of congestion is also noted.

Intestine.—Superficial epithelium eroded; lumen filled with cells; these cells are—many polynuclear, others with atypical nuclei of many forms; the cells are in all likelihood granulation tissue; owing to the contraction of the muscular layers, the granulation cells appear to fill the entire lumen; the epithelial cells in the fundi of the crypts appear normal; the submucosa and muscular layers are normal in appearance. In other sections this granulation tissue has replaced entire glands.

RAT IX, SERIES I.

AUTOPSY FINDINGS.

Lungs normal; heart normal; liver dark; spleen dark; kidneys congested; small intestine hemorrhagic.

MICROSCOPIC APPEARANCES.

Lungs.—Tissue extremely congested; in some areas red blood cells are seen in the alveoli; all alveolar walls are thickened as a result of this congestion; the characteristic pigmentation is present; the alveoli are distorted and walls broken.

Liver.—Congestion of central and portal veins; mild congestion of intralobular capillaries; pigmentation of many liver cells, also granular degeneration of others.

Spleen.—Typical congestion and pigmentation of the pulp; in many instances this pigmetation can be traced into the Malpighian bodies. The pigment consists of both hemosiderin and hemoglobin. The former is abundant.

Kidneys.—Congestion of all glomeruli and interstitial capillaries; cytoplasm of cells of urinary tubules granular and broken.

RAT X, SERIES I.

AUTOPSY FINDINGS.

Lungs normal; heart congested; liver dark; spleen dark; kidneys congested; nothing abnormal in gastro-intestinal tract.

MICROSCOPIC APPEARANCES.

Heart.—Muscle fibers pale, stain faintly, transverse striations not seen; the sarcoplasm is very granular.

Lungs.—Slight congestion and the characteristic pigmentation, otherwise tissue appears normal.

Spleen.—Pigmentation and congestion of the pulp.

Kidneys.—Characteristic granular degeneration in the cells of the urinary tubules.

SUMMARY OF CELLULAR CHANGES OCCURRING IN WHITE RATS, SERIES I.

Lungs.—Extreme congestion and in some cases edema and hemorrhage; extreme pigmentation, much of which is hemosiderin and consequently a vital process; the alveolar walls are thickened as a result both of congestion and interstitial cellular growth; in many instances the proliferation and congestion has resulted in complete compaction of large areas. Lymph cell infiltrations, surrounding the larger vessels and bronchi, are much greater than are seen in normal rats.

Heart.—In only one case was the heart preserved, this stains but faintly; the transverse striations have completely disappeared; the sarcoplasm is granular.

Liver.—In every instance there is seen congestion of the central and portal veins; in most cases the intralobular capillaries are congested—the degree of congestion varying with different animals—in some cases it approaches the nutmeg type; depending upon the degree of congestion, alterations are observed in the liver cells; where the intralobular capillary congestion is extreme, there is seen atrophy of liver cells, granular changes in the cytoplasm, albuminous degeneration; many cells are pigmented—hemosiderin as well as hemoglobin. As a rule no fatty infiltration is seen.

Spleen.—Shows extreme congestion and pigmentation of the pulp substance; the pulp cells in every instance are practically filled with hemosiderin granules; this is readily differentiated from the precipitated hemoglobin by potassium ferrocyanide and hydrochloric acid. In many cases there has been an active proliferation of the pulp substance and as a consequence the Malpighian bodies are much decreased in size—in some instances only a few lymphoid cells remain.

Kidneys.—A moderate degree of congestion is generally seen; in practically every instance cytoplasmic disturbances have occurred in the epithelium of both the urinary and collecting tubules; the most pronounced disturbances are seen in the convoluted tubules; these alterations are granular cytoplasm and broken or eroded epithelium in which the proximal ends of the cells have completely disappeared; other changes are vacuolations and reticulations (hydrops).

Intestines.—Only in Rats VII and VIII was this tissue preserved. Both show erosion of the epithelium and evidences of an active proliferation of the connective tissue cells of the mucosa; in VIII areas are seen where the entire glands are replaced by this granulation tissue and fibrin, ulcers.

3. WHITE RATS, SERIES II.—TISSUE ALTERATIONS RESULTING FROM STARVATION.[1]

Series II (three rats) shows the changes that the tissues undergo as a result of starvation-withholding of foods. That the previous diets of bread and milk, before fasting was begun, did not affect the tissues is seen in the report of the Normal Rat. In a rat whose diet consisted solely of cracked corn only slight alterations are observed. Reports of the latter two rats will precede that of Series II.

NORMAL RAT.

Fed on bread and milk; age 2½ months; is in good condition; killed by chloroform; born of mother also fed on bread and milk.

AUTOPSY.

Everything normal.

Tissues from the lungs, liver, spleen, and kidneys were fixed in both Zenker's solution and formalin. All proved to be normal and were frequently used for comparisons with other tissues.

FULL-GROWN RAT.

Fed on cracked corn for 3½ months; age 7 months; killed by chloroform; is emaciated, otherwise normal.

AUTOPSY.

Heart and lungs normal; liver slightly congested; spleen normal; kidney mottled, contracted, and red; pyloric part of stomach hyperaemic; intestines normal; central nervous system normal.

MICROSCOPIC APPEARANCES.

Lungs.—Show congestion, lymphoid cell infiltration; many alveolar walls thickened.

Liver.—Slightly congested, the liver cells are somewhat granular.

Spleen.—Slightly pigmented, however, this is hemoglobin, it does not react to Perl's test.

Kidney.—Slightly congested.

RAT I, SERIES II.

Fed on milk and wheat bread from September 18, 1914, to January 2, 1915. No more food allowed. Water given. Body weight, 210 gm. January 19, dead at 2 p. m. Weight, 108 gm.

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[1] The starving rats were kept in glass jars containing sawdust. It is not excluded that these animals ate some sawdust.

MICROSCOPIC APPEARANCES.

Heart.—Transverse striations indistinct, intense congestion of all blood vessels.

Lungs.—Extremely congested, the alveolar walls bulge out into the sacs as a consequence of the congested tortuous capillaries.

Liver.—Extremely congested; only the peripheral cells of the lobules persist; those cells located centrally have disappeared; as the cord of cells is followed from the peripheral end to the center of the lobule, they become more and more vacuolated, fatty degeneration, then atrophic, and finally disappear.

Spleen.—The typical picture of the entire series is seen here—the reduction of the lymph areas and extreme congestion of the pulp, together with numerous large endothelial cells filled with red blood cells and pigment. The later, however, is chiefly hemaglobin, although hemosiderin is present.

Kidneys.—Extreme congestion of all vessels. The cells of the urinary tubules are swollen; the cytoplasm is granular and stains faintly. Pigment is present, but it is hemoglobin and not hemosiderin.

Esophagus and cardiac end of stomach.—Congestion of submucosa.

Central nervous system.—Sections from the cerebrum did not show any pronounced changes; large Betz cells were not seen in this section. The cord was vacuolated throughout, suggesting extreme edema. The anterior horn cells presented different forms of nuclei; some were large and vesicular, others again were small and the chromatin filled the entire nucleus. The cytoplasm suggested that chromatolysis had occurred but, as this tissue was fixed in formalin, the degree of chromatolysis could not be as definitely ascertained as could have been done in other fixations—alcohol. Evidence also was present which suggested degeneration of the superficial portions of the posterior tract. Unfortunately no tissues were prepared by the Pal-Weigert method.

SUMMARY.

Extreme congestion of both thoracic and abdominal organs; edema and apparent degeneration of tracts and cells in the cord.

RAT II, SERIES II.

Fed on milk and wheat bread from September 18, 1914, to January 2, 1915. No more food allowed after latter date. Water given. Body weight, 223 gm. January 11, 1 p. m., convulsions, marked hyperexcitability. January 15, found dead at 8 a. m. Weight, 112 gm.

MICROSCOPIC APPEARANCES.

Heart.—No transverse striations seen; sacoplasm swollen and granular; no pigmentation observed.

Lungs.—Alveolar capillaries and all vessels intensely congested and thickened; many alveolar sacs are filled with blood cells.

Liver.—Liver is moderately congested; fine pin-point areas of lymphoid cell infiltrations are seen throughout the section; cytoplasm of liver cells is somewhat granular.

Spleen.—The congestion of the pulp is not so pronounced as in this organ in Rat I, although congestion occurs here. The Malpighian areas are encroached upon by the congested pulp, which contains numerous enlarged endothelial cells.

Kidneys.—Extreme congestion of all blood vessels; the glomeruli and interstitial capillaries are intensely congested. The cells of the urinary and collecting tubules are swollen, the cytoplasm is granular.

Stomach.—No pathological changes are observed.

Central nervous system.—Cerebrum is congested, the vessels of both the pia and cortex are distended with blood; no changes are observed in the nerve cells.

Cord.—The cells of the anterior horn are large—apparently swollen—and chromatolysis has occurred. Many large vacuoles are present in both the gray and white matter. As described elsewhere in other sections, the nuclei of the anterior horn cells are variable—some are large and vesicular, others, again, are comparatively small and stain solidly throughout. An apparent diffuse degeneration of tracts has occurred. The cord is intensely congested.

SUMMARY.

Pronounced congestion and cellular changes in practically all the thoracic and abdominal viscera; congestion, chromatolysis, and degeneration of tracts in the central nervous system.

RAT III, SERIES II.

Fed on milk and wheat bread from September 18, 1914, to January 2, 1915. No more food allowed after this date. Water given. Body weight 102 gm. Died at 4.45 p. m., January 10. Weight 58 gm. Stomach empty; bloody fluid in small intestine.

MICROSCOPIC APPEARANCES.

Heart.—Striations indistinct; sarcoplasm granular. In some cells vacuoles are seen—fatty degeneration. All vessels are congested.

Lungs.—Intense congestion of the alveolar walls which are much thickened.

Liver.—Both central and portal veins intensely congested; this congestion extends between the liver cords; the cytoplasm of the liver cells is to some degree granular and atrophic, especially in those cells in closest proximity to the central veins; many of the latter are vacuolated—fatty infiltration.

Pancreas.—Appears normal.

Spleen.—The capsule is thickened; the Malpighian areas are reduced in size. Throughout the pulp, numerous red blood cells are seen showing marked passive congestion; much hemosiderin is present and numerous red blood cells are found within large swollen endothelial cells.

Esophagus and stomach.—The submucosa of the cardiac end of the stomach intensely congested. In that region of the stomach which contains gastric glands, complete erosion of the epithelium had occurred; only the connective tissue elements of the mucosa remains, the surface of which is covered with fibrin. Between the crypts formed by the connective tissue mucosa, elongated threads and plugs of mucin still persist. The submucosa and mucosa, likewise, are necrotic in certain areas; one area shows a typical ulcer formation. (See Figs. 15 and 16.)

Kidney.—Congestion occurs in all vessels; the cytoplasm of the urinary tubules in particular stain faintly; the glomeruli appear normal.

Skin.—A section from this tissue is normal in appearance, except for a small area of pigment the nature of which was not determined.

Cerebrum.—Pia is slightly congested, spaces occur between the pyramidal cells and the surrounding cortex; this may be due, however, to the fixation.

Chromatolysis has occurred in many of these cells. An invading tumor from the meninges is seen in one area, which is very cellular and in nature suggests sarcoma.

Spinal cord.—All vessels are congested.

SUMMARY.

Congestion of all organs of the thoracic and abdominal viscera with evidences of nutritional disturbances of the parenchyma of these organs; in the central nervous system congestion occurs and the pyramidal cells of the cortex have undergone chromatolysis.

SUMMARY OF CHANGES IN SECOND SERIES OF WHITE RATS.

In making a complete summary of the changes observed in the White Rat, Series II, it will be noted that these animals had lost approximately 50 per cent of their weights in periods ranging from 8 to 17 days. The microscopic changes are as follows: Heart—albuminous degeneration, congestion; lungs—extreme congestion and hemorrhages, in many instances the alveoli are filled with blood; liver—extreme congestion, cloudy swelling, fatty degeneration, partial to total atrophy of liver cells; spleen—prominent capsule, trabeculae, appear very much thickened, extreme congestion, reduction in areas to complete disappearance of Malpighian follicles as a result of this congestion and hyperplasia of endothelial cells, the latter are filled with red blood cells and pigment hemoglobin and hemosiderin; kidneys—extreme congestion of all vessels both of the glomeruli and intertubular capillaries, albuminous degeneration; gastrointestinal tract—congestion, hemorrhage, erosion of epithelium, ulcerations, atrophy; central nervous system—pia congested; cerebrum congested, pyramidal cells show chromatolysis and are swollen; cord congested, edematous, anterior horn cells swollen, chromatolysis, nuclear disturbances, degeneration of nerve fibers in the posterior tract, slight and diffuse degenerations in other tracts.

When Series II is compared with Series I one finds that the pathological changes in both are very similar. In Series I much more hemosiderin is found, while fatty degeneration, as seen in the liver, is less frequent. In Series II the congestion is far more pronounced.

4. PIGS—DIETS OF CORN-OIL CAKES.

PIG NO. 1.

Fed on corn-oil cake meal for eight months. Marked ataxia appeared after some time. Animal became emaciated and refused part of food. Extract of autolyzed yeast was without effect on the condition of the animal, which died after having been completely paralyzed.

AUTOPSY FINDINGS.

Emaciated body; skull very brittle, spongy, but not red; brain soft; cord soft; lungs, right lung shows some edematous patches, left lung normal; heart in systole, no dilatation of right heart, very little clear pericardial fluid; liver congested; gall bladder filled with pale bile; spleen small, dark red, and congested; pancreas normal; kidney small; stomach fundus hemorrhagic; duodenum slightly injected; ileum hemorrhagic; large intestine normal, filled with fluid fecal matter; ribs, marrow intensely red; some of the teeth are loose (scurvy?); femur, pale marrow. "This animal showed some signs of scurvy," remarks Prof. Voegtlin, "although they were of very doubtful nature. Perhaps a histological examination will throw some light on this question."

MICROSCOPICAL EXAMINATION.

Heart.—Transverse striations are indistinct, sarcoplasm is granular, the individual fibers are widely separated, congestion of blood vessels. The sympathetic nerve cells seen in this section stain very faintly and appear swollen. No pigmentation is present.

Lungs.—Alveolar walls are thickened and congested; many alveoli contain numerous large round cells with one or more nuclei, the cytoplasm of these cells is prominent and stains deeply with eosin, some of these contain red blood cells. These cells are undoubtedly endothelial cells of the alveolar walls. Certain areas show infiltration of polymorphonuclear leucocytes around the bronchioles-bronchiopneumonia. Marked congestion occurs throughout.

Thymus.—Somewhat congested; one area is seen in which an irregular mass of deep brown pigment and shadows of red-blood cells are present. The pigment gives only a slight hemosiderin reaction.

Liver.—Intense congestion exists. The central veins are especially congested; this congestion extends into the lobules between the liver chains; many of the latter are broken; those cells in closest proximity to the central veins are atrophic and the cytoplasm is granular.

Spleen.—Extreme atrophy of the cellular elements and hypertrophy of the connective tissue substance—the capsule and trabeculae are much thickened. The Malpighian areas are reduced to minute points. The pulp is composed chiefly of large endothelial cells filled with red blood cells and pigment—hemosiderin. (See Figs. 17 and 18.)

Kidney.—Glomeruli are intensely congested; this is true of all the vessels.

Stomach.—Submucosa is slightly congested, otherwise the section is normal.

Duodenum.—A small ulcer is present, the surface epithelium is for the most part eroded and a hypertrophy of the connective tissue elements of the mucosa has taken place. A marked congestion is seen throughout the section.

Jejunum.—Mucosa and submucosa are intensely congested. The muscular wall is very thin. In many areas complete erosion of the superficial epithelium has occurred.

Bone.—An apparent increase of the connective tissue elements of the marrow has occurred.

Nervous system.—Cerebrum—In formalin fixed tissue, the pyramidal cells are shrunken and spaces exist between them and the matrix. This same picture is seen in the alcohol-fixed tissue although the cells are not so much shrunken; Nissl's granules are very indistinct—an apparent chromatolysis has occurred. In some of these cells, minute vacuoles are seen. Larger vacuoles are seen in the white substance.

Cerebellum—Purkinje cells are faintly stained and are deeply embedded in molecular layer.

Medulla—No pathological changes are observed.

Cord, cervical—No changes are observed in the anterior horn cells.

Cord, dorsal—Many of the anterior horn cells appear swollen, are pale, and chromatolysis has occurred. Interesting in connection with this reaction are the large vesicular nuclei. In many sections of formalin fixation so far studied the nuclei stain deeply and solidly throughout, similar to the nuclei of many epithelial cells. It was surmised that this condition was due to the action of the fixitive—formalin. However, in this section—fixed in formalin—the nuclei are large and vesicular. Whether these changes in the chromatin of the nuclei as seen in various sections of this series are due to the fixatives or are pathological changes has not been determined.

The white matter contains numerous vacuoles indicative of edema. These vacuoles are seen in the horns in alcohol fixed tissue. A suggestive degeneration more or less diffuse has occurred. No Pal-Weigert's preparations were made, however, so this could not be accurately determined from the sections at hand.

Spinal ganglion.—These cells stain more faintly than the normal.

Sciatic nerve.—Normal so far as could be determined by this section.

SUMMARY.

Gross appearances.—Emaciated body; skull brittle; brain and cord soft; right lung edematous; liver congested; spleen small and congested; gastrointestinal tract congested and hemorrhagic.

Microscopic findings.—Heart congested, transverse striations absent, sympathetic nerve cells in heart swollen, and stain faintly; lungs congested; thymus congested, pigmented; liver extremely congested; spleen atrophic, pigmented hemosiderin; kidney congested; gastrointestinal tract congested, superficial epithelia eroded; ulcer in duodenum; central nervous system more or less chromatolysis of pyramidal and anterior motor horn cells with suggestive changes in the nuclei of the anterior horn cells, no pigmentation. Apparently degeneration of spinal cord tracts has occurred but unfortunately, due to fixatives used, this could not be accurately determined.

PIG NO. III.

Initial weight 29 pounds; was fed corn-oil cake meal beginning with March 10; after several weeks animal developed constipation, feces were hard and black in appearance; during June animal showed symptoms of paralysis; no edema could be noticed; no symptoms of scurvy; during the following weeks the animal alternately improved and got worse; died October 16.

AUTOPSY.

Heart in systole, right ventricle slightly edematous, no dilatation of right heart; right lung partly consolidated with tuberclelike masses; smears taken from lung by Dr. Stimson show no tubercle bacilli; liver dark red; spleen small and slightly dark; kidneys slightly congested; stomach hemorrhagic; mesenteric glands enlarged; ileum hemorrhagic; duodenum shows very thin walls; large intestine contains greenish-black feces, shows some injected areas; pancreas slightly hyperaemic; brain normal; spinal cord soft; skull and spine brittle; teeth are not loose; skeletal muscles normal; no hemorrhagic areas; no signs of scurvy.

MICROSCOPIC FINDINGS.

Heart.—Transverse striations still visible but rather faint; blood vessels all congested; no pigmentation present.

Lungs.—This section presents a typical picture of pneumonia; all alveoli are filled with fibrin and polymorphonuclear leucocytes; the vessels are intensely congested; two small sharply defined necrotic areas are present surrounded by polymorphor cells.

Spleen.—This organ shows pronounced changes. The lymph cell areas, Malpighian, have almost completely disappeared; the capsule and trabeculae are especially prominent; the pulp is composed almost entirely of large endothelial cells which are filled with red blood cells and hemosiderin pigment. The walls of the central arteries are thickened. (See Figs. 19 and 20.)

Pancreas.—Congested; pigmented areas occur; some of this pigment reacts to potassium ferrocyanide and hydrochloric acid, hemosiderin.

Kidney.—Many of the glomeruli are vacuolated, much desquamation of epithelia of urinary and collecting tubules has occurred; the vessels are congested; no pigmentation is present.

Stomach.—Superficial epithelium is eroded; the submucosa is intensely congested.

Small intestine.—Mucosa, submucosa, and muscularis are intensely congested; muscular wall in certain areas is atrophic.

Skin.—Sections of this tissue appear normal; a small degree of congestion is present in the subcutaneous vessels.

Central nervous system.—Sections of the cord fixed in alcohol show dilatation of the central canal and chromatolysis of the anterior horn cells. In many instances the nuclei of these cells stain solidly throughout instead of being vesicular.

Sciatic nerve.—As far as could be determined by the fixation—alcohol—the nerve is normal.

SUMMARY.

Gross appearances.—Heart, right ventricle edematous; lungs consolidated; liver congested; spleen dark, atrophic; kidneys slightly congested; stomach hemorrhagic; mesenteric glands enlarged; ileum hemorrhagic; duodenum atrophic; pancreas slightly congested.

Microscopic findings.—Heart congested and slight degenerative change in muscle fibers; lungs congested, pneumonia; pancreas congested and traces of hemosiderin; spleen atrophy of Malpighian areas, pulp atrophic, congested and pigmented, hemosiderin; gidney shows degeneration, degenerative changes in epithelium of urinary and collecting tubules, also congestion; gastrointestinal tract shows desquamation of superficial epithelium, congestion, and atrophy of muscular walls; spinal cord shows chromatolysis of anterior horn cells and nuclear changes.

SUMMARY OF CHANGES IN PIGS.

The pathological changes in the pigs may be briefly summarized as follows:

Autopsy findings: Emaciation; conditions that resembled scurvy; skull brittle; brain soft; cord soft; lungs edematous and consolidated; heart edematous; liver congested, dark red; pancreas hyperemia; kidney congested, atrophic; retroperitoneal lymph glands enlarged; gastrointestinal tract congested, hemorrhagic, atrophic; spleen atrophic, congested.

Microscopic changes: Heart loss of striations to pronounced albuminous degeneration, congestion; lungs extreme congestions with herzfehlerzellen and blood cells in the alveoli, consolidation and pneumonia with its characteristic pathological changes; thymus pigmented and congested; liver intense congestion, liver cell cords interrupted as a result of this congestion, albuminous degeneration and atrophy of liver cells; spleen capsule and trabeculae prominent as a result of atrophy of the pulp, Malpighian follicles greatly reduced both in area and numbers, pulp congested, hyperplasia of endothelial cells which are filled with red blood cells and pigment, abundant hemosiderin; pancreas pigmented and congested; kidneys intense congestion, albuminous degeneration, vacuolization of the glomeruli; gastrointestinal tract congested, hemorrhagic, ulcerated; bone marrow pronounced proliferating activity; central nervous system, cerebrum vacuolated due to edema, chromatolysis and vacuoles in the pyramidal cells; cerebellum Purkinje cells very faint in their staining reaction; cord evidences of a mild and diffuse degeneration in all tracts, chromatolysis and vacuolation of anterior horn cells; spinal and sympathetic ganglion cells stain very faintly.

5. RABBIT—TISSUE CHANGES DUE TO ALUMINUM LACTATE ADMINISTRATION.

The following record shows the effect of prolonged administration of aluminum lactate on body tissues. The cellular changes are not unlike those reported by Von Doelken.

RABBIT NO. IV.

Fed on cabbage and whole wheat; received daily, with the exception of Sundays, 80 milligrams of aluminum lactate per stomach tube, beginning August 3. Animal lost considerable weight and died October 2.

AUTOPSY.

Heart and lungs normal; peritonael cavity contains some bloody fluid; liver dark brown; spleen congested; kidneys congested; large intestine shows intensely hemorrhagic areas with small ulcers; small intestine shows thin walls, otherwise normal; stomach filled with undigested cabbage and wheat; fundus shows injected area; brain appears normal; cord soft.

MICROSCOPIC APPEARANCES.

Heart.—Extremely congested, striations very indistinct, sarcoplasm granular.

Lungs.—Congestion throughout, alveolar walls bulge out with congested capillaries. In many areas the sacs are completely obliterated.

Liver.—Only slightly congested.

Spleen.—Typical congestion. The Malpighian areas are reduced; the pulp is filled with red blood cells and hemosiderin. Large endothelial cells are numerous and filled with pigment and red blood cells.

Pancreas.—Only slightly congested.

Kidney.—Glomeruli are intensely congested. Congestion of all interstitial capillaries is prominent. The cells of the urinary tubule are granular.

Stomach.—The mucosa is congested; the submucosa and muscularis are atrophic; the individual fibers of the muscular coat are widely separated.

Intestine.—Intense hemorrhage into the mucosa; only here and there remnants of the epithelium are seen. The muscular coat is vacuolated (hydropic) and atrophic, in some areas only a meshlike layer of connective tissue fibers containing congested blood vessels remain in its place. (See Fig. 21.)

Cerebrum.—The pia is congested, also areas of round cell infiltrations are seen in this structure; the pyramidal cells are swollen, stain faintly, many of the nuclei are eccentric in position; the vessels of the cerebrum are congested throughout.

Cord.—The anterior horn cells have been greatly disturbed as they are finely and diffusely granular; the nuclei in many of these cells have disappeared. Vacuoles also appear in many of these cells. Larger vacuoles are seen in both the gray and white matter. A diffuse degeneration of fibers in the tracts is observed.

SUMMARY.

Gross findings.—Peritoneum contains dark fluid; liver dark; spleen congested; kidneys congested; stomach injected; small intestine atrophic; large intestine hemorrhagic and ulcerated; cord soft.

Microscopic findings.—Extreme congestion throughout thoracic and abdominal viscera with nutritional disturbances in the parenchymatous cells; hemorrhage, congestion, atrophy of muscular walls, and disappearance of epithelium are characteristic of the gastrointestinal system; central nervous system chromatolysis and nutritional disturbances of motor cells, edema of gray and white matter, and diffuse degeneration of tracts.

CONCLUSION.

From this report one readily sees the close similarity of the cellular changes due to chronic aluminum lactate poisoning and those alterations already considered resulting from malnutrition—starvation by withholding food or from food deficient in some essential constituent. That no specific pathological alteration can be attached to aluminum poisoning seems very probable. On the other hand, that the cellular alterations are due to nutritional disturbances as a consequence of a circulating toxic principle appears to be the case because of the resemblance of cell changes.

Before discussing the various cellular alterations as observed in our series of experimental animals the tissue changes in pellagra will be considered. As already intimated the pathological changes in the former simulate the latter in practically every respect. After pellagra is considered both will be discussed together.

PART II.—CELLULAR CHANGES IN PELLAGRA.

1. LITERATURE.

In the following references I have included the principal contributions on the pathology of pellagra. For a more complete bibliography of the most important of the numerous contributions on all phases of pellagra the reader is referred to Babcock and Lavinder's translation of Marie's La Pellagre.

Spessa (1) describes opacities in the arachnoid and adhesions of the meninges.

Hanneau (2) states that inflammation, hemorrhages, and ulcers are usually found in the stomach—observed by Strambio also. He further states that Brierre, of Boismont, in 1829 did five autopsies, finding congestion, hemorrhage, and ulcers of the stomach, and injection of the meninges, brain, and cord, with softening of the cord. Similar observatons on the whole were made by Landouzy in 1852, and by others.

M. Bouchard (3) describes changes in the liver, heart, and spinal cord of a pellagra case. Fatty degeneration of the liver was observed: the heart showed both fatty degeneration and infiltration with acetic acid resisting pigment in the sarcoplasm; the cord degeneration was not confined to any specific tract, both the internal and posterior portions of the posterior tract and the external portion of the lateral columns were the seats of pronounced alterations; congestion of the vessels of the cord and sclerosis of the cord were noted; numerous amyloid bodies were found throughout both the white and gray matter.

Verga (4) describes inflammation of meninges; congestion of meningeal vessels; osseous deposits in the meninges; constant alterations in the cord, softening or induration of both substances; and atrophy or degeneration—more especially in the dorsolumbar region.

Ch. Bouchard (5) summarizes the pathology of pellagra as found in Gintrac's Traite de Pathologie as follows: The skin is shiny, delicate, dense like parchment and a thickening at the borders of the erythema is seen; the latter has sometimes a brownish tint or is more often decolorized; the cranial bones are thickened; the dura is very adherent to the cranial bones and to the brain; the falx contains numerous ossifications, the vessels here are engorged; the arachnoid is thickened; the vessels of the pia are injected; hydrocephalus is present, as evidenced by dilated ventricles; the brain may be normal, firm, more often soft; the cerebellum is injected, indurated or soft; atrophy of the medulla has been found and softening of the
more often in the lumbar region; various alterations
described in the lungs, such as inflammations,

may be independent of pellagra; the heart is flaccid; congestion, hemorrhage, and inflammation of the gastrointestinal tract are present; in one case the pancreas was enlarged; the liver is usually large; the spleen may be large, small, soft, or indurated.

Billod's (6) conclusions are as follows: (a) That softening of the spinal cord is as frequently observed in the insane who have had pellagrous erythema as in the others. (b) That this same softening is not observed as frequently in the pellagrous insane as the casual result of his first observation led him to suppose. (c) That the pellagrous insane that do not show these softenings, are, in general, the patients in whom the disease had had a more rapid course and has early terminated in death. (d) That the nonpellagrous insane who have this softening in question are the patients who have been for a more or less considerable period in a state of cachexia more or less profound and who required only the erythema to be classified as pellagrous.

Bassi (7) describes alterations in various organs. According to him the heart shows brown atrophy and fatty degeneration of the muscular fibers; the ganglia of the cervical sympathetic system show pigmentation, fatty degeneration, and atrophy; the skin is sclerotic and thinned. He found upon consulting other records that more than one-half the cases of pellagra died from intercurrent diseases. But in the acute cases—typhoid pellagra—he was constrained to place the cause of death on the condition of the respiratory organs. According to him the lungs were always edematous and occasionally in the state of gray hepatization; the pneumonia, however, instead of being either distinctly lobar or bronchial, was more of the type of aspiration pneumonia or like that obtained by Friedlander after cutting the vagi nerves. The air sacs were filled with lymphoid cells, red blood cells, and fluid. Bassi found no appreciable lesions in the vagi nerves of pellagrins, but noted changes in the medulla which might be responsible through the vagi for pneumonia. These changes were gray degeneration of the nerve substance beneath the ependyma which covers the floor of the fourth ventricle in the region of the alae cinerae. The dura resembled pachymeningitis hemorrhagica interna acuta.

In transverse sections of the cervical spinal cord Bassi found a marked proliferation of the ependyma of the central canal and in the gray substance of one of the anterior horns he found three very large vessels with sclerosed walls such as are found in tabes dorsalis; scattered through the gray substance were numerous amyloid bodies.

rne (8) described lesions observed in the cutaneous nerves. degeneration of the myelin sheaths was present in two ns were at the site of the exanthema, and he concludes that the skin lesions in pellagra are due to trophic disturbances of nerves.

Hirsch (9) summarizes the alterations in pellagra as follows: Hyperaemia and inflammation of meninges, liver, spleen, and lower intestinal tract; atrophy and marasmus, particularly of those organs innervated by the vagi and the sympathetics; fatty degeneration of different organs; pigment metamorphosis.

Tonnini (10) contributes an extensive paper to the pathology of pellagra. According to him, in the progressive orders of frequency the following lesions have been observed: Subarachnoid hemorrhage in 4 cases and anemia of the membranes, accompanied by severe anemia of the cord in 8 cases; hyperemia of the cord in 15 cases. Opacities, thickenings, and adherence of membranes and osteomata are present. The latter is more frequent in pellagrins than in nonpellagrins. To these osteomata Tonnini attaches considerable significance, for according to him they may be responsible for the spasticity and heightened reflexes observed in some pellagrins. Osteomata are found almost exclusively in the posterior and posterior lateral tracts and chiefly in the lumbar region. In the spinal cord the following alterations are described by Tonnini: (a) Asymetry of the two halves with granular pigmentary degeneration and cellular atrophy and degeneration of tracts. (b) Hyperemia, which is always associated with that of the membranes. Punctate hemorrhages were also seen. This hyperemia is found more frequently in the lumbar region and is responsible for the feeling of increased resistance to touch—hardness. (c) Diminution of weight. In male pellagrins the cord was slightly less, while in female pellagrins the cord averaged at least 3 grams less in weight. (d) Softening: In every case this is a simple nonphlogistic softening and not red softening. It can not always be differentiated from that due to post-mortem changes. In some of these the vessels were occluded. Many granule cells were observed in the nervous tissue, and the axis cylinders were in stages of dissolution. It was difficult to differentiate between the gray and white matter in fresh sections. Edema was always associated with softening. (e) Anemia was frequently present. Microscopic examination of the cord showed intense pigmentation of both the anterior and posterior horns, which obscured the nuclei of nerve cells and in some instances the entire cell. This pigmentation is the most frequent microscopic finding. Lombroso and Bareggi had described pigmentation of sympathetic and spinal ganglion cells, but none heretofore had noted it in the horn cells. Atrophy of nerve cells was also noted by Tonnini as well as degeneration of lateral columns and posterior columns. Hence the microscopic findings in the cord are numerous and varied. These changes are different from those produced in ergotism.

De Hieronimis (11) claims to have observed in cases of pellagra a very pronounced small-cellular (*parvicellulare*) infiltration of the gray substance and the white substance of the cord; he also found infiltration around the ependyma, enlargement of the perivascular and percellular lymphatic spaces, together with increase of the cephalo-arachnoidian fluid. In the central canal he noted partial endothelial proliferations of the ependyma, and corresponding to these points, in the adjacent periependymal gray substance, he noted inflammatory foci. These lesions were not constant in the different contiguous sections, but disseminated.

Marchi (12) described, in two cases of typhoid pellagra, changes consisting of degeneration of many fibers in the anterior lateral tract, diminution of the interweaving fibers in the anterior cornua, and marked pigmentary degeneration of the spinal and sympathetic ganglia. Marchi does not place much importance on the pigmentary degeneration of nerve cells, as this has been found in conditions other than pellagra. Fatty degeneration of the renal epithelium is also referred to by him.

Belmondo (13) contributes a detailed record of changes observed in the spinal cord in 20 cases of pellagra. These alterations were leptomeningitis, ossific arachnitis, pachymeningitis. Degeneration and scleroses of the crossed pyramidal tracts—a constant condition—and of the columns of Goll and Burdach were found. These lesions are found chiefly in the dorsal and lower cervical regions. Constant alterations are found in the gray matter as well, namely, atrophy of the motor horn cells with increase of pigment. Belmondo regards these pathological changes as primary degenerations due to intoxication, the toxin having a special affinity for the pyramidal tract. The infective agent is introduced into the gastrointestinal tract.

In connection with the pathological alterations Belmondo discusses the clinical symptoms, which are paraparesis (sometimes a true hemiplegia), exaggeration of the muscular tone and increase of the tendon reflexes, paralytico-spastic gait, tremor, and uncertainty of movements in the upper extremities. The censory alterations are not uniform.

Tuczek (14) studied the spinal cord in eight cases of pellagra. There were changes in all. Only in two cases was the posterior tract alone involved, while in six cases both the posterior and posterior lateral tracts had degenerated. In the former the median fibers were chiefly involved, while those next to the gray matter were normal. Of the posterior lateral tract fibers, the cerebellar tracts were normal, while the pyramidal tract fibers were those involved. According to Tuczek the spinal cord changes in pellagra stand between posterior tract degeneration and lateral sclerosis. These changes simulate similar lesions due to ergotism, alcoholism, and other intoxications. Belmondo, however, held that the spinal symptoms in pellagra have little in common with ergotism, and that the anatomical symptoms likewise would support this view.

Neusser (15) found in one case of pellagra atrophy of the heart and liver, chronic catarrh of the stomach and intestines, subacute nephritis, induration of the retroperitoneal lymph glands. Microscopically the brain, cord, and sympathetic system were normal. In the second case Neusser described fatty changes in the heart, kidney, and liver, chronic catarrh of the gastrointestinal tract, and in the dura of the cervical enlargement, a condition of pachymeningitis interna which caused disturbances of muscular nutrition and skin of the upper extremities.

Lombroso (16) gives the results of his observations on 113 autopsies conducted on pellagrins. In the meninges he found opacities, thickenings, hemorrhagic extravasations, and purulent exudates; in the cerebrum, softening, atrophy, scleroses, hyperemia, anemia; in the cerebellum, sclerosis, softening, edema. According to him, these findings agree with those of Marchi, Fanzago, Strambio, Verga, Rizzi, and Morelli. In the spinal cord, Lombroso states that the posterior roots of the spinal cord are affected, and that the lesions in the spinal cord simulate incipient tabes, except that few changes are seen below the dorsal region. In Babcock and Lavinder's translation of Marie's La Pellagra are found in more or less detail the pathological changes in other organs as described by Lombroso. These changes are similar to those described by other observers and are in general the various types of cell degeneration and retrogressive changes. These cellular alterations are by no means constant, but vary in different individuals.

Schreiber (17) conducted autopsies on 14 individuals who had died of pellagra. According to him, the most constant findings were: (*a*) Erythema—observed on the skin in 3 cases; in all of the other cases it was present in other portions of the body. In only 1 of these cases was the skin of the hands affected with swellings and excoriations. (*b*) Intense anemia, general or partial dropsy. (*c*) Stomach and intestinal affections—in 8 cases, chronic catarrh; in 2, superficial ulceration; and in 1, dysentery. (*d*) Changes in the central nervous system—in all cases, intense anemia; in 7 cases, simple serous edema of the brain and spinal cord; in 5 cases, serous softening of the brain around the ventricles, containing much serum, and at the base. These were the cases in which during life mental disturbances were manifested. The spinal cord in 3 of these cases were serously softened; in 2 cases, only in the posterior columns; and 1 case, in its entire upper half. With regard to the other pathological findings—in 1 case peritonitis was present, which in this case was probably the cause of death as an intercurrent infection; in 7 cases tuberculosis was present; in 8 cases the liver was enlarged (fatty degeneration); in 3 cases, atrophy of the liver (cirrhosis); in 6 cases, spleen enlargement; in 4 cases, spleen atrophy and fatty degeneration of the kidneys; and in 1 case, contracted kidney.

Babes and Sion (18) observations may be summed up as follows: Muscle tissues atrophic, pigmented; bone embryonic tissue persisting and Charcot Leydig crystals in the marrow; mouth gingivities with ulcers, hemorrhagic infiltration of gums; tongue atrophic, round cell infiltration; intestines atrophic, hyperemic, desquamation of superficial epithelium; lymph glands swollen, degenerated; liver atrophic, pigmented, fatty degeneration, congested, occasionally enlarged; spleen atrophic, pigmented; kidneys atrophic, granular, fatty changes rarely; heart soft, atrophic, friable, brownish color; aorta atheromatous plaques; blood anemia, poikilocytosis, reduced erythrocytes; amyloidosis of finer vessels; skin trophoneurotic disturbances, thickening of corneal and Malpighian layers of skin, erythema, hyperemia, edema; dura chronic irritative changes; pia edema, injection, pigmentation; nervous system degeneration of posterior tract including the columns of Goll and Burdack, degeneration of posterior roots and Clark's column. According to Babes and Sion, Lissaur's zone as well as the most anterior fibers of the posterior tract are less often affected in pellagra than in tabes. A similar observation had previously been made by Marie (19). Of nerve cells, those in Clark's column are always affected; pyramidal cells of cortex show chromatolysis, pigmentation; similar changes were present in anterior horn cells. In typhoid pellagra, the greatest changes are found in the gastrointestinal tract, central nervous system, and the skin.

Tizzoni and Fasoli (20) report the cultivation of a strepto-bacillus pellagræ from pellagrin blood smears. See also Tizzona (21). This was verified by Wood, but Lavinder found no such organism in smears obtained from various tissues taken from pellagrins.

Regarding the blood picture in pellagrins, much has been written. Noteworthy among the contributions are Buhlig (22), Lavinder (23), Siler and Nichols (24), and Bybee (25). Lavinder's article contains a review of other work done on the blood in this disease. His conclusions are: (*a*) That there seems to be present in pellagrins a fairly constant secondary anemia, usually not a severe type in the red blood cells. (*b*) That leucocytosis is rarely seen and is probably not a phenomenon of uncomplicated pellagra. (*c*) That the results obtained by various workers on differential leucocyte counts are very discordant and that conclusions should be drawn therefrom with much hesitation, though a relatively large mononuclear increase seems probable. (*d*) That nothing resembling a protozoal parasite has been observed. (*e*) Blood of South Carolina pellagrins is uniformly sterile as shown both in culture media and laboratory animals. He has not been able to isolate Tizzoni microorganism.

Harris (26) calls attention to the difficulties encountered in the study of pellagra pathology because of extreme chronicity of disease—exacerbations of the disease being frequently mistaken for acute cases, patients rarely die in earlier stages of the disease, intercurrent maladies frequently take patients off and as a consequence the morbid anatomy of the two diseases confounded—no instance of pathology of single uncomplicated case of pellagra in the earlier stages, but on the other hand, all studies have been made on old complicated pallagrous tissue. He predicts the future will show that the initial changes are in the central nervous system.

In the report of the Pellagra Commission of the State of Illinois (27) nothing specific was found in the pathological studies of pellagrous tissue. Its findings may be summarized as follows:

Nervous system: Axonal chromatolysis of nerve cells in praecentral convolutions, cells of nuclei in pons, cerebellum, medulla and posterior roots of cord and sympathetic ganglia. Many of these cells showed pigmentary degeneration and fatty changes similar to that found in senile nervous systems; little evidence of connective tissue proliferation. The picture resembles central neuritis.

Liver, constant seat of low grade inflammation of portal connective tissue lying in the interlobular septa; the intralobular capillaries engorged and in most cases many small blood extravasations; peripheral fatty degeneration; intestines, ulcerations in 3 out of 7 cases, no amoebae, low grade infiltration of the mucosa and submucosa; kidney, degenerative changes in renal epithelium, more or less interstitial nephritis, some of these in young cases, enlargement of capillaries and small hemorrhages in some cases; spleen, fibrous overgrowths and some small hemorrhages; heart, pigmentary changes in heart muscles at an age below that usually found—in some cases hyalin changes in intima of blood vessels.

The report concludes that: Evidently some toxic substances originating from the gastrointestinal tract are in the blood; these pathological changes may be secondary to pellagra, that is, as a result of metabolic disturbance, invasion of other agencies from gastrointestinal tract; this is no evidence of parasitic causes, except in the liver and gastrointestinal tract; the nervous system does not present any features similar to trypanosomiasis and parasyphilis because of absence of focal changes and perivascular infiltrations; the skin lesions are not due to post root involvement as the distribution of the lesion does not correspond to post root distributions. "Pellagra is sometimes described as a disease especially involving the nervous system. From the findings here described the nervous system seems to be involved only as a secondary process and at a late stage of the disease, in this respect confirming the opinion expressed above from clinical study."

An interesting suggestion is that made by Wilgus (28) that the neuritis of pellagrins is similar to the neuritis described by Meyer (29). The latter found in 8 patients dying from exhaustion changes in Betz cells—haziness of the protoplasm, displacement of Nissl's bodies and axonal degeneration. Regarding this similarity, Wilgus states: "After having seen the symptoms described under the heading Central Neuritis (by Adolph Meyer) and then witnessing the symptoms noted as occurring in the terminal stages of pellagra it was not difficult to conclude that these terminal symptoms in pellagra were identical with those of Meyer's Central Neuritis. In other words, pellagra has central neuritis as a terminal condition, as a rule. Of course I am speaking here of the clinical side alone. Meyer believed this condition to be based on some toxic state, and suggested that alcoholism was frequently the basis on which central neuritis developed. After seeing cases of pellagra one can readily agree with him in his general conclusion that central neuritis is due to toxemia."

Niles (30), in his book on pellagra, refers to Dr. Sandwith's report on the pathology found in pellagra. According to the latter there is general cachexia and anemia; the skin showed exfoliation, atrophy, diminution of subcutaneous fat; the heart, liver, and spleen were atrophic; the lungs contained tuberculous lesions; intestines, erosions of superficial epithelium, atrophy of the muscular coats; cord showed degeneration of posterior tract and roots; Golls column was most affected. According to Niles, Thrash performed four autopsies on pellagrins. The findings were, in general: In acute cases—hyperemia and cloudy swelling of all organs. In chronic cases—atrophy, vacuolization, degeneration of nuclei, brown atrophy of visceral cells were the rule; the brains showed cell degeneration in the cortex, followed by sclerosis; spinal cord, degeneration and sclerosis of posterior and lateral tract.

Roberts (31) and Wood (32) summarize the pathological findings in pellagra.

Owing to the fact that so many contributions have appeared on this subject, I have been forced to omit many references which should perhaps be included. Mention is made of Strambio (33), Vassale (34), Liberali (35), Procupiu (36), Raubitschek (37), Valtorta (38), Guyot (39), Amabilino (40), Spiller and Anderson (41), and Brugia (42), who have contributed to our knowledge regarding cellular changes in pellagra.

Summary of literature.—From the extensive literature on this subject, the cellular alterations as observed by others may be summed up as follows:

Heart—softening, albuminous degeneration, fatty infiltration and degeneration, brown atrophy, congestion.

Lungs—edema, congestion, pneumonia, tuberculosis.

Aorta—atheromatous.

Liver—enlarged, atrophic, fatty degeneration, hyperemia, inflammatory.

Spleen—atrophy, enlarged, congestion.

Pancreas—generally normal, rarely enlarged.

Kidneys—atrophic, cloudy swelling, congestion, pigmentation.

Gastrointestinal tract—congestion, hemorrhagic, ulcerated.

Meninges—congestion, hemorrhagic, adhesions, opacities, osteomata.

Brain—injection, induration, softening, degeneration of pyramidal cells.

Cord—degeneration chiefly in crossed pyramidal tract and in columns of Goll and Burdach. These lesions are located most frequently in upper thoracic and lower cervical; however, they have been described at various levels. Pigmentary degeneration of spinal ganglion cells, anterior horn cells, sympathetic cells. Amyloid bodies in cord have been described.

Skin—atrophy, hypertrophy, erythema, exfoliation, etc.

Bones—fragility, embryonic marrow.

Pigmentary degeneration: in heart, liver cells, cerebral vessels, in addition to that described in the nervous system.

2. TISSUE CHANGES IN PELLAGRA AS OBSERVED IN THIS LABORATORY.

I have had the opportunity of studying the microscopic changes in a number of cases of pellagra. For the clinical histories and reports of gross morbid findings, I am indebted to various members of the United States Public Health Service who have within recent years confined their attention to the study of pellagra. The tissues were obtained from the hospitals at both Savannah and Spartanburg.

Only two complete clinical histories are included in this report, as these represent the typical cases.

The following records do not include all my observations respecting cellular changes in this disease, but include only representative cases. It was soon seen that the tissue alterations in all pellagrous cases observed were with slight variations very similar and that they resembled those described by other investigators. For this reason I have not included an extensive report of all tissues examined, nor have I included among the plates photographs of these alterations, as the numerous treatises and reports on pellagra are abundantly illustrated with them.

As previously intimated, my chief interest was to determine, if possible, whether there is a specific and distinct pathology to this disease and if a specific organism is present that might be related to the disease. The results of this phase of the work are included after the report on the general tissue changes. In submitting this brief report of the general tissue changes, no claim is made that this represents any additional contribution to our knowledge of the pathology of pellagra. My purpose is simply to make a comparison of these cell alterations with those already described in the experimental animal series.

CASE B. G. NOTES, CLINICAL AND AUPTOPSY, BY W. F.

HISTORY OF THE CASE.

Past history.—Admitted to the hospital March 21, 1914. Information obtained from husband. Born in Columbia, S. C., in 1872. Age 42. One child living, age 24. One child dead, cause unknown. Unable to read or write. Husband, special officer of the Central Railroad. Father, farmer, a periodical drinker. Patient's usual health was good until two years ago, since which time it has been declining, although patient did her housework until about a month ago, at which time she went to bed, remaining there a day or so, and then returning to work, which condition continued until two weeks ago. Then the patient developed an acute excitement and was placed in jail, since which time the acute excitement continued. In bed, apparently from exhaustion. Usual weight 145 pounds, present weight 90 pounds. Nothing known of either paternal or maternal grandparents, except they lived to be old. Father living, in good health; one maternal cousin said to have become insane; six brothers in good health; one sister killed accidentally; mother died at 40, probably insane for two or three years, said to have died from tuberculosis. Statement was made that the mother's condition was very much like patient's present condition. Birth of patient was difficult, instruments were used. General health in infancy good. As a child, was obedient and cheerful. Attended school but very short time. Husband does not know why patient did not learn at school. Six years ago had some vaginal operation performed at Savannah.

Present illness.—Just before the insanity began, it was noticed that patient would be blue and downhearted for a day or so and would be irritable and cross. No previous attack. Her memory before insanity very good; since it developed, memory has been poor. About a month ago, patient spoke of suicide, remarking that she had rather be dead than alive. Just before being placed in jail, she tried to hit her husband with her fist. At times she spoke of having considerable money—this was during the excitement. The month previous to insanity she at times said that her food did not smell nor taste right and complained of headache in frontal portions of head at irregular intervals during last six months. During last six weeks slept very poorly. Appetite very poor. Patient had two miscarriages, one several years ago, one about four years ago, cause of this unascertained.

Physical examination.—Many teeth missing; complexion sallow; panniculus scant; muscles flabby; mucous membrane very red and inflamed; on posterior surfaces of hands extending about 8 or 10 cm. up the wrist is the characteristic darkened, reddening of pellagrous eruption with scaling; this scaling is more marked on the dorsal surfaces of the fingers; over the second and third joints, the skin is very much roughened and thickened; this condition is bilateral and symmetrical; the darkened discoloration is also over the posterior surfaces of elbows and along the course of the ulna nerve. Anterior surface of ankles show slight thickening and roughening; some roughening and scaling on toes. Eyes sunken; conjunctivæ anemic; pupils dilated, react to light, reaction rather sluggish; smell, sight, taste, and hearing could not be satisfactorily examined, neither could sensibility. Deep reflexes active. No clonus. Tremors not apparent. Speech showed no characteristic defect. Bowels constipated, according to history. Tongue appears red and deeply fissured. Abdomen rigid, boardlike.

Mental examination.—Patient brought to ward on stretcher, apparently very feeble. Lies in bed, inclined to follow in a vague way any movement that goes on about her. Talks to herself, and throws her hands, muttering at times in a very indistinct voice something about wanting water. Occasionally she will reiterate the same word in a monotonous tone until it becomes quite indistinct. She obeyed a few simple commands, such as opening her mouth, shutting her eyes for tremors, etc. Upon several occasions she referred to the physicians and nurses as "Pa." When asked where she was, she looked at the physician in a confused manner, opened her mouth and popped her teeth together several times. When asked what day it was, she said it was the 4th of July. "Where is your home?" "Pa." Many questions that were asked were not replied to. Patient continues to look about the room muttering some unintelligible words. It was evident that patient was in a delirious condition. Occasionally noticed to be very restless, drawing up her legs and arms. At such times tremors are noticed. She will move about in bed from side to side. Will permit flies to light on her face and make no effort to remove them.

March 24, 1914.—Within the last 24 hours the dorsal surfaces of hands and wrists became a pinkish color. This condition is bilateral and symmetrical.

Staff meeting.—Diagnosis: Pellagrous insanity, infective-exhaustive type.

March 30, 1914.—Patient confined in bed. Sleeps very irregularly. Rolls about from side to side picking at cover. Entirely oblivious to surroundings. Never speaks any intelligible words. Bowels very loose. Urine must be obtained by catheter. Face is frequently contorted. Lips are chapped. Tongue very much reddened. Saliva dribbles from corners of mouth on pillow. Patient pays no heed to questions nor does she assist in any way with her care.

April 17, 1914.—Patient has continued in delirious state formerly described. Picks at bedclothes. Coarse jerky tremors of the upper extremities are present. At no time has any intelligible reply been obtained to questions. She has developed a very marked odor; the red appearance of the skin has subsided, but left a scaly, darkened, roughened skin over the areas formerly involved. Bowel and urine discharges pass unheeded. Takes liquid nourishment when fed. Very evidently in a marked delirious state; that is, the appearance of a severe typhoidal state.

POST-MORTEM EXAMINATION.

Died at 6.10 a. m., April 24, 1914. Post-mortem at 7.45. White female. Extremely emaciated, showing slight bedsore formation over sacrum. Pupils equal 2.5 mm. diameter. Body still warm.

Roughened scaly skin over back of hands extending 6 cm. up the forearm and encircling the wrists. Small areas over both elbows posteriorly roughened and scaly, somewhat discolored. Small skeleton. On sections muscles very anemic. Abdominal and thoracic viscera normal with exception of liver, which extended about 6 cm. below the border of the ribs. Both lungs are free of adhesions, normal in appearance. Right lung shows some edema and congestion in its lower lobe posteriorly.

Heart negative with exception of pale muscles and apparently slight increase of fibrous tissue in myocardium. Aorta shows small patches of atheroma.

Spleen considerably enlarged, slight increase of consistency. Both kidneys show nothing other than slight cloudy appearance on sections. Capsule stripped quite readily.

Liver appears enlarged and pale in color. Consistency about normal. Suprarenals normal in appearance. Stomach somewhat dilated, contains about 10 ounces of fluid. Mucosa hyperemic. Mucosa of duodenum appears hyperemic. Mucosa of ilium shows areas of very marked hyperemia. Mucosa of colon shows areas of petechial hemorrhages.

Uterus enlarged, due to several small fibroids. Tubes and ovaries normal in appearance, latter somewhat sclerosed. Pancreas normal in its appearance, somewhat enlarged.

Brain: Scalp negative. Dura negative. Vessels of pia are injected. No gross lesions of the brain discernible. Spinal cord appears rather small and fairly firm. Vessels of the pia are injected.

Sections taken from frontal, precentral, and calcarin areas of right cortex; from both lungs, both kidneys, spleen, liver, suprarenals, stomach, duodenum, ileum, colon, and pieces of both ulna nerves placed in 10 per cent formalin.

Weight of organs: Brain, 960 grams; cerebellum, 130; cord, 29.5; left lung, 170; right lung, 270; heart, 180; liver, 1,020; spleen, 190; pancreas, 170; left kidney, 120; right kidney, 120.

MICROSCOPIC FINDINGS.

Myocardium.—The muscle fibers are atrophic; the transverse striations are indistinct and in many cells can not be made out; there is a marked increase of brown pigment within the cells—in many instances extending the entire length of the cell—brown atrophy; many cells possess vacuoles—fat; the nuclei did not stain deeply.

Lungs.—Sections of this tissue show that a state of chronic passive congestion has existed for some time; all vessels are distended with red blood cells; a pronounced proliferation of connective tissue has occurred; as a result many of the alveoli have been completely replaced by this tissue. The connective tissue is very cellular, composed of both lymphoid and epithelioid cells—the former predominating; the walls of many alveoli are thickened; this thickness varies from a slight increase to complete occlusion of the alveoli; frequently the walls are seen to be ragged and broken; numerous "herzfehlerzellen" are seen both within the vascular lumina and in the connective tissue new growths. Much pigment (carbon) is seen in the lymph spaces.

Liver.—The section plainly shows that the liver has undergone atrophic changes; many lobules can be seen in the same field; the atrophic changes are most pronounced in those cells proximal to the central veins; here the cells are flattened—atrophic and wide intercellular spaces are seen; these cells possess much fine brown pigment—brown atrophy. As one approaches the periphery of the lobules the cells become more normal in structure; the pigment decreases and the intercellular spaces become narrower, gradually disappearing. Numerous large globules of fat are seen in the periphery of the lobules, especially around the portal veins.

Spleen.—The capsule appears thickened; the trabeculæ are prominent; the walls of the blood vessels are thickened—especially is this true of the arteries. The Malpighian follicles are decreased in size, being limited as a rule to a narrow zone around the arteries. There is relative increase of spleen pulp as compared with the follicles. The pulp is composed for the most part of large endothelial cells filled with red blood cells and pigment; numerous pigment granules are seen both intra and extra cellular. The section simulates that of beginning senile atrophy and passive congestion. Van Gieson's stain shows a more pronounced prolifieration of connective tissue cells, especially from the capsule and trabeculæ. No hyalin changes, however, are seen. No amyloid substance is present.

Pancreas.—Cells are shrunken and broken; in all likelihood this is a postmortem change.

Kidney.—This section of the kidney shows slight changes. The capsule is slightly thickened and congested; the stellate veins are congested, which is also true of the glomeruli and the interstitial vessels; the cells of the uriniferous tubules show a granular condition of the cytoplasm; the nuclei are normal in staining characteristics. No basal striations are seen in proximal convoluted tubules; the collecting tubules are normal in appearance; no increase of interstitial connective tissue was observed.

In another section the capsule is thickened and torn in many places from the cortex. In various areas extreme congestion of all the vessels is present. The glomeruli are filled with red blood cells, some are sclerotic, others hyalinized. Between the collecting tubules elongated areas of congestion and hemorrhage can be made out. A characteristic feature of this section is the pigmentation. This minute dark-brown pigment is present within the vessel lumina, the interstitial tissue around large blood vessels, and the epithelia of both the uriniferous and collecting tubules, and is especially abundant within the hemorrhagic areas. For the most part it is hemoglobin, as it does not react to Perls test.

Suprarenals.—No distinct pathological changes can be made out. The cells of the cortex, especially the zona fasciculata contain much lipoid substance; much pigment is also seen in the cells of the zona reticularis. These conditions, however, are not distinctly abnormal. The medulla appears normal; an accessory suprarenal is present. In Van Gieson's stain the capsule appears slightly thickened; a slight increase of the connective tissue framework appears to have taken place.

Stomach.—Pyloric end—all surface epithelium gone. Mucosa very cellular, containing numerous plasma cells; mucosa very congested, which is also true of the atrophic submucosa and mucularis. The muscular layers are very thin.

Jejunum.—Surface epithelium eroded; epithelium and goblet cells in bottom of crypts are normal; mucosa congested; submucosa and tunica muscularis atrophic.

Colon—Superficial epithelium is eroded; these cells, as well as the goblet cells, are well preserved in the fundi of glands; the mucosa otherwise appears normal. There is a pronounced atrophy of both the submucosa and muscular layer. The blood vessels are congested. In many sections crystaloid substances can be made out in the epithelium. No pigmentation is observed.

Cerebral cortex.—A small piece of cerebral cortex, as well as a cross section of the sciatic nerve, was prepared. No degeneration tracts were observed in these after staining with Pal-Weigerts.

Dura.—In one particular area there is a focal chronic pachymeningitis consisting of new connective tissue and numerous blood vessels; the dura is not congested.

Pigment—Heart, spleen, kidney, liver. Tests were made for hemosiderin in these tissues with the well-known Perl's test—potassium ferrocyanide and hydrochloric acid. The pigment in these tissues did not react as a rule to this technique, consequently these granules for the most part are not hemosiderin. In the kidney, minute areas of iron-reacting pigment were found under the capsule and in the collecting tubules, both within the epithelial cells and blood vessels. In sections of these tissues, fixed in formalin and stained by Herxheimers, the pigment gave no reaction.

SUMMARY.

Gross findings.—Extreme emaciation; roughened, scaly skin on back of hands; anaemic muscles; right lung edematous and congested, especially lower lobe; heart pale, aorta atheromatous; spleen enlarged; kidney cloudy; liver large, pale; gastrointestinal tract hyperemic, colon contains petechial hemorrhages; pancreas somewhat enlarged; pia over brain is injected.

Microscopic appearance.—Heart brown atrophy, fatty degeneration; lungs passive congestion wtih herzfehlerzellen; liver atrophy, fatty degeneration; spleen sclerotic capsule and trabeculae, extreme passive congestion; kidney passive congestion, slight albuminous degeneration of the cells in the uriniferous tubules, hyaline changes are seen in many glomeruli; suprarenals normal; stomach congestion and atrophy of muscular walls; jejunum and colon superficial erosion of epithelium, congestion, atrophy; cerebrum and sciatic nerve show no degenerations of tract; dura congested, focal pachymeningitis.

CASE T. H.—CLINICAL AND POSTMORTEM NOTES BY W. F.—ADMITTED TO HOSPITAL MARCH 3, 1914.

HISTORY OF THE CASE.

Past history.—Information obtained from husband and patient. Family: Mother died at 40 following childbirth; father living, said to be insane; nothing known of grandparents; one paternal uncle said to be insane. Personal: Patient 43 years old; healthy as child; said to have been a normal child; attended school irregularly; menstruated at 15; married at 20; married life congenial; always healthy, with the exception of the history of pellagra; four children living; labor unaccompanied by any abnormalities.

Present illness.—Patient states that for about 15 years every spring or twice a year her hands would become red, as if sunburned; occasionally had an attack of diarrhea; condition would clear off, and patient would feel quite well between attacks; during last few years she lost weight progressively. She referred to the skin condition as "erysipelas." Denies ever having any mental trouble previous to the present, nor did her husband notice any. In September last year her hands again became red and scaly; at that time had sore mouth and diarrhea.

Physical summary.—Examination made March 6, 1914, three days after admission. Poorly nourished white female, showing considerable anemia; pallor of mucous membrane, thickened, discolored scaly skin over posterior surfaces of hands extending up the forearm about 8 cm. and encircling wrist; tongue presented a sleek appearance; deep reflexes all equally exaggerated; slight diarrhea present; subjective complaints of nervousness, burning of skin; pupils normal; no disturbance of cutaneous sensibility; muscular strength much reduced.

Mental summary.—Patient appeared depressed when interviewed, frequently wept, talking in an indistinct whining tone of voice, answers questions quite relevantly, seats herself in a rather dejected, uncomfortable manner, restlessly picking at her dress or fingers. Frequently questions must be repeated. Cleanly in her habits; at times appears apprehensive, especially when alone in her room. Takes very sparingly of food; sleeps three or four hours of the night. Never associates with other patients. Remains in bed the greater part of the time; makes few requests. Has not learned the names of physician and nurses, and makes no inquiries. Begs to be allowed to go home. Expresses a few ideas of persecution, believing that poison had been placed in her food and milk. Claims that God has spoken to her at times, and that she has seen her children. Claims that she is very much frightened; says that she is afraid something is going to happen to her and her children. Admits she is down-hearted and blue. Is disoriented for place; does not recognize the character of the institution, other than it is some kind of hospital. Does not know the day of the week, but knows the month. Does not recognize the physician, but mistakes the examiner for another physician to whom she has spoken the day before. Her memory for recent events is very poor; believes that she has been at the hospital five days, when in fact she has been here but three. Knows she came on train, but has a very meager recollection of her trip to the hospital or what transpired soon after her reception. Her memory for remote events was much better. Patient was able to name her school-teachers and recalls events of her earlier life. Her grasp in general was in accord with her opportunities and station in life. Patient's mental calculation was performed slowly. She could not continue at a simple problem for any length of time, claiming that she became exhausted and could not think as she wanted to. Her retention of test words and numbers was defective. She had some insight into her condition; thought that there was something wrong with her mind; remarked that she could not collect her thoughts and keep them together, that her memory was poor at times, and that she frequently felt very confused.

Note, March 23, 1914.—The patient showed very little change in her mental and physical condition up until two days ago, when she became restless, very confused; at that time did not recognize the examiner or nurse, was entirely out of contact with her surroundings, muttered and mumbled to herself in an unintelligible manner. Coarse jactitory tremors of arms and legs were pronounced. Dorsal surfaces of hands and skin encircling wrists appeared very red and inflamed with scaly desquamation over reddened areas. Tongue very brightly red, gums and mucous membrane also showed reddishness. Bowels constipated. Patient did not understand questions that were asked her. At one time referred to the examiner by some name familiar to herself. Bowel and bladder control lost. Emaciation and anxious expression on the face quite apparent. Pulse, 110. Temperature, 97.8.

Note, March 26, 1914.—Patient continues in stuporous state, during which she could not be made to understand any questions and was entirely lost to her surroundings. She grew progressively weaker, muscular twitching and jerking became more pronounced. Died at 2 a. m., brought to post-mortem table at 9 a. m.

POST-MORTEM EXAMINATION.

Post-mortem examination made seven hours after death. Somewhat emaciated, scaly dermatitis over both hands posteriorly and encircling wrists; over both elbows, posteriorly darkened, roughened, scaly skin symmetrically situated; similar patches over sacrum. Pupils equal, 3 mm. Post-mortem discolorations over dependent portions of the body. Rigor mortis present in both extremities. On section, small amount of subcutaneous fat. Abdominal viscera in normal position. Thoracic viscera normal position. Both lungs negative, excepting slight edemia and congestion at the bases. Heart, 275 gms., showed nothing abnormal other than the muscle was pale and flabby and the valve flaps very slightly thickened. Aorta showed slight amount of atheromatous degeneration. Spleen somewhat congested, weight 120 gms., somewhat firmer than normal, slightly increased amount of connective tissue. Liver weighed 1200 grams, was pale and anemic, had cloudy appearance, central veins rather prominent, consistency about normal. Right kidney, 155 grams; nothing abnormal, capsule slightly adherent, entire organ rather pale. Left kidney, 200 grams, presented same appearance and condition; suprarenals negative. Uterus fibrous and slightly enlarged. Small intestines negative, with the exception of a few areas of congestion in the mucosa of the ilium. Large intestine congested, patches 6 to 8 cm. in diameter in the mucosa, in some instances very marked. In areas of congestion a granular appearance was noted. These patches were irregularly distributed throughout the colon. The remaining viscera showed nothing abnormal to the eye. Skull of normal thickness. nothing abnormal noted in scalp; edematous piamata; apparent increase of cerebrospinal fluid; adhesion between pia and dura in the neighborhood of longitudinal sinus slightly more marked than normal; pial vessels slightly congested and pia strips from brain very readily; no areas of softening or gross changes were observed; basal vessels normal in appearance. Cord: No gross abnormalities were observed; in region of the fourth lumbar interspace a perforation of the dura with a slight ecchymosis surrounding perforation was noted. (Patient was punctured at this site.) Piece of tissue taken from heart, liver, large intestine, kidney, brain cortex (parcentral lobe and frontal lobe), spinal dura, both ulnar nerves, and spleen.

MICROSCOPIC APPEARANCES.

Heart pericardium.—Five cm. thick; fatty infiltration with large congested blood vessels.

Myocardium.—Hypertrophied, considerable increase of interstitial connective tissue; myocardial muscular fibers in many instances segmented and fragmented; transverse striations for the most part distinct, slight amount of pigment at poles of nuclei—brown atrophy.

Tissues from the heart were fixed in formalin, sections were made by the frozen method and stained by Herxheimer's method. On examination of a section through the left ventricle the pericardium is found to be 0.5 cm. thick, due to the large amount of fat. This fat had infiltrated along the blood vessels and interstitial tissue into the myocardium. In the latter globules of fat are observed more or less irregularly distributed throughout the myocardium, especially in the connective tissue surrounding blood vessels. Fat globules are also present between the muscular fibers—these vary in size, but are usually larger than white blood cells. Within the sarcoplasm of many cells exceedingly fine fat granules are also seen. The endocardium is normal.

Liver.—Lobules indistinct but relatively large; the presence of congestion is evidenced by numerous erythrocytes seen between the liver cells; these cells, however, are not atrophic; the nuclei stain distinctly; considerable brown pigment is seen in the liver cells, especially those more centrally located; the portal veins are distended with blood.

Tissues fixed in formalin, sectioned by the frozen method and stained by Herxheimer's method. Practically all liver cells are filled with exceedingly fine fat globules, uniformly distributed throughout the entire gland. In many cells one large droplet of fat (undoubtedly the result of confluency of the smaller droplets) alone was seen occupying the entire capacity of the cell.

Stomach.—Epithelium is completely eroded; submucosa is very much congested; muscular layer is normal.

Kidney.—The capsule is slightly thickened; the glomeruli appear normal; the cells of the convoluted tubules are somewhat granular. The vessels throughout are congested. No abnormal pigmentation is observed.

Cerebrum.—The pia is thickened; its vessels are distended and congested; the cortex is congested.

SUMMARY.

Gross findings.—Case T. H. Somewhat emaciated; skin scaly, roughened dermatitis over exposed portions of hand and wrist; lungs slightly edematous and congested; heart pale and flabby; aorta atheromatous; spleen congested and firm; liver atrophic, pale, anemic, cells cloudy; kidneys congested, cloudy degeneration; suprarenals normal; small intestines contain few areas of congestion in ileum; large intestines, few areas of congestion; pia edematous and congested.

Microscopic appearances.—Heart, extreme fatty degeneration and infiltration; liver, congestion and pigmentation; stomach, erosion of epithelium and congestion; kidney, congested.

Nervous tissue from cases B. G. and T. H. was not available for microscopic examination. It was used for chemical analysis.

Tissues from the following cases were obtained at the United States Public Health Service Hospital at Savannah. The writer does not have in his possession notes regarding the clinical histories and post-mortem gross findings. However, these were much similar to the two cases just considered and represent the usual histories and post-mortem reports found in pellagrins, especially in the pellagrous insane.

CASE NO. 8.

MICROSCOPIC APPEARANCES.

Heart.—Endocardium is thickened; an increase of subpericardial fat is observed; the transverse striations are indistinct but still can be made out; characteristic brown atrophy is present; an increase of connective tissue is noted throughout the section.

Lungs.—The pleura is thickened; a typical picture of chronic passive congestion is noted; the alveolar walls bulge out and appear thickened as a consequence of distended tortuous capillaries. In many areas the alveoli are filled with "herzfehlerzellen" large endothelial cells filled with red blood cells; in addition to these, edematous substance fills the alveoli; much carbon pigment is present.

Liver.—The capsule is slightly increased in thickness; an increase of the connective tissue elements is noted throughout, which is plainly seen in Van Gieson's stain; congestion of all vessels is present; the intralobular capillaries are distended; the liver cells in closest proximity to the hepatic veins are atrophic and flattened as a consequence of the distended capillaries; these cells possess numerous fine amorphous brown granules which do not react to Perl's test—hence hemosiderin is not present.

Kidney.—The capsule is thickened; a general connective tissue increase is found throughout the section; the glomeruli are sclerotic and hyalin bodies are found within them; the cytoplasm of the cells of the convoluted tubules are granular and a detritis fills the lumina; hyalin bodies are found within many of these cells.

Spleen.—The capsule is thickened, an increase of connective tissue is noted throughout the section; the trabeculæ are very prominent; the pulp is congested, numerous red blood cells are seen; large endothelial cells, filled with red blood cells and a greenish brown pigment—hemosiderin—are especially prominent; the central arteries are in many instances sclerosed and hyalinized; hyalin bodies are seen in the reduced Malpighian areas.

Lymph gland.—Contains numerous hyalin bodies.

Spinal cord.—Cervical region an irregularly spherical new growth of glial cells immediately behind and bordering the commissure and between the posterior horns. The lesion does not reach the posterior surface and consequently does not supplant the entire posterior tract. Both columns (Goll and Burdach) are entirely destroyed immediately behind the commissure, but both are continuous at the posterior or superficial surface. The cells of this lesion are composed of more or less round or oval nuclei, which possess as a rule one nucleolus surrounded by deep staining chromatin granules. The nuclei average 5 μ in diameter. The cytoplasm is composed chiefly of a fine fibrillar net work. No cell boundaries are observed. At the periphery of the growth irregular radiating fibers from these cells extend into the white matter, between the neighboring medullated axones. The center of the lesion has undergone degeneration—liquefaction—only fibrin and a few nuclei remain. This new growth is undoubtedly glial in nature and apparently has had its origin from the ependymal cells lining the neural canal. The fibrils of these cells stain blue in Mallory stain.

In that portion of the posterior tract not directly affected by the lesion are seen, irregularly distributed, small round homogeneous bodies averaging 15–20 μ in diameter. These stain blue in Bensley's Neutral Gentian and were first observed by the application of this stain. They were also observed in other tracts. They are not numerous. These bodies are also stained blue in haematoxylin and eosin. Some show deeper stained substances within, but these substances are not present with any degree of regularity. I do not consider these bodies of any special significance. They are either amyloid, hyalin bodies, or droplets of myelin. No specific staining reaction of these bodies was obtained.

Unfortunately all tissues of this case had been fixed in Zenker's solution, and, as a consequence, it was impossible to determine accurately the degree of degeneration of the remaining portion of the posterior, lateral, and anterior tracts.

The nerve cells of the gray matter had undergone no pathological changes so far as it was possible to determine. The above lesion was limited to the cervical region. Its extent there, however, was not determined, although it appeared in two segments removed below this.

Dorsal region.—Tissues taken from two regions of the thoracic portion of the cord do not show this type of lesion. Here a few of the above described bodies are seen in the white matter. The cells of the anterior horn and gray matter in general appear normal.

SUMMARY.

Microscopic appearances.—Heart, fatty infiltration, fibrosis, brown atrophy; lungs, pleura thickened, extreme passive congestion; liver passive congestion, fibrosis, atrophy, and pigmentation of liver cells; kidney fibrosis, congestion, sclerosis, and hyalinization of glomeruli, albuminous degeneration of cytoplasm of convoluted tubules; spleen, increase of connective tissue of capsule and trabeculae, extreme passive congestion; spinal cord, a gliosis as seen in the cervical region which has resulted in an almost complete degeneration of both the columns of Goll and Burdach, only the posterior peripheral fibers are intact. Hyalin or amyloidlike bodies are found in the posterior tract.

No specific significance is attached to either the glial proliferation or these bodies.

CASE P.

The tissues from this case were fixed in Zenker's solution and formalin and embedded in paraffin.

Heart.—Endocardium thickened; transverse striation indistinct; the nuclei, however, are normal in the staining characteristics.

Liver.—No distinct changes observed.

Spleen.—Extreme passive congestion, the lymph cell areas reduced in size; the pulp is relatively increased; numerous red blood cells are found in the pulp. A hyperplasia of the endothelial cells of the pulp has occurred—these are filled with red blood cells.

Kidney.—Capsule is thickened, the stellate veins are congested; this is true of the vessels throughout; no changes are observed in the epithelial cells of the tubules.

Spinal cord.—Thoracic region—pia appears normal; peripheral fibers of both the posterior and lateral tracts appear degenerated; the white matter is vacuolated throughout; the anterior horn cells are normal in appearance.

Sections from the cervical and lumbar regions show similar picture to that described for the thoracic region.

No changes are observed in the spinal ganglia cells.

CASE W.

Liver.—A general cirrhosis throughout the section is noted; the liver cells are atrophic and pigmented, this is especially evident of those cells closest to the central veins; those cells which occupy the periphery of the lobule are vacuolated, fatty degeneration or infiltration; the original liver cell cords are broken up into islets and separated from each other by connective tissue.

Spleen.—Capsule is thickened; extreme congestion is present throughout; the Malpighian bodies are reduced in area; the pulp is especially prominent and filled with red blood cells and endothelial cells.

Kidney.—Convoluted tubules are for the most part dilated; the cytoplasm of these cells are granular and a detritis is seen in the lumina; an increase of connective tissue is noted, especially is this true in the glomeruli.

Spinal cord; cervical region.—Congestion is seen in the vessels of both the gray and white matter. The pyramidal tract has completely degenerated; a degeneration of the marginal fibers of the posterior tract is also present; the cells of the anterior horn appear normal.

CASE R. K.

The tissues from this case consisted entirely of spinal cord and were prepared according to Pal-Weigert's method.

Cervical region.—The pyramidal tract is slightly degenerated; degenerated fibers are diffusely distributed throughout this tract.

Thoracic region.—Here many diffuse degenerated fibers are seen in the posterior tract as well.

Lumbar region.—Fewer degenerated fibers are seen in the posterior tract than in the thoracic region.

CASE T. W.

Spinal cord prepared according to Pal-Weigert's method.

In the cervical and dorsal levels of the cord only a diffuse marginal degeneration was noted in the posterior and lateral tracts.

Tissues from other pellagrins were examined, but the histological findings were not dissimilar to those already described and consisted in general of passive congestion of practically all the viscera with degeneration of the parenchymatous tissue of the various organs.

SUMMARY.

The tissue alterations in pellagra, as observed in this laboratory, may be summarized as follows:

Gross changes.—Extreme emaciation; exposed surface of skin scaly, roughened, dermatitis; muscles anemic; lungs congested and edematous; heart pale and flabby; aorta atheromatous; spleen enlarged, congested; kidney cloudy; liver large, pale, atrophic, anemic; gastrointestinal tract hyperemia, petechial hemorrhage; pancreas somewhat enlarged; pia injected.

Microscopic findings.—Heart—fatty degeneration, fatty infiltration, brown atrophy, fibrosis; lungs—passive congestion, fibrosis; liver—extreme passive congestion, fatty degeneration and infiltration, pigmentation, atrophic and broken liver cell cords, fibrosis; spleen—extreme congestion, atrophy, thickening of trabeculæ and capsule, reduction in areas and numbers of the Malpighian follicles, hyperplasia of endothelial pulp cells which contain ingested pigment and shadows of red blood cells; kidneys—passive congestion, albuminous degeneration, hyalin changes, sclerosis of glomeruli and interstitial tissue; gastrointestinal tract—congestion, superficial erosions of epithelium, atrophy of muscular coats; dura—congestion and pachymeningitis; cord—gliosis in posterior tract with degeneration of the columns of Goll and Burdach, degenerations of pyramidal tracts, diffuse degenerations in other tracts, numerous small amyloid or hyalin bodies, congestion of both white and gray matter.

Conclusions.—These findings are very similar to those observed by other investigators (see summary at end of literature on pellagra, p. 40). My findings differ only in the degree of pigmentation which is so emphasized by others. I failed to find the pronounced pigmentation of nerve cells reported by many observers.

In attempting to determine whether there were present any cell alterations that might be regarded as specific to pellagra, or any organism that might be a specific etiological factor, the following technique was used:

1. Sera from pellagrins was examined by the—

(*a*) Dark field illumination.
(*b*) India ink method of Burri.

2. Tissues prepared by—

(*a*) Levaditis method.
(*b*) Giemsa's method.
(*c*) Stimson's method for staining Negri bodies in section.

3. Numerous fixation solutions were used in addition to alcohol, formalin, and Zenker's solution. Among these were:

(*a*) Modified Kopsch formalin bichromate solution—

Formalin 40 per cent, 1 part; $K_2Cr_2O_7$ 3 per cent aq. sol., 3 parts; 1 part	1 part
Sat. sol. of $HgCl_2$ in 95 per cent alcohol	1 part
Distilled water	2 parts

(*b*) Bensley's sublimate alcohol bichromate solution—equal parts of saturated solution $HgCl_2$ in 95 per cent alcohol and 2½ per cent aqueous solution of $K_2Cr_2O_7$.

(*c*) Formalin bichromate solution, neutral formalin 10 c.c. and Zenker's solution without the acetic acid 90 c.c.

(*d*) Acetic osmic bichromate solution:

$K_2Cr_2O_7$, 2½ per cent aqueous solution	8 c.c.
Osmic acid, 2 per cent	2 c.c.
Glacial acetic acid	1 drop

These various fixations are in special use among histologists for the purpose of preserving and demonstrating the finer structures of cells—structures that are not generally preserved in the standard fixation solutions such as alcohol, Zenker's, and formalin. Sections from these specially fixed tissues were stained in numerous dyes used for the demonstration of normal and abnormal cell structures. The stains utilized were: Geimsa's, Leishman's, Wright's, Herxheimer's, Van Gieson's, Weigert's elastic tissue stain, muchaematein, mucicarmin, methyl-violet for amyloid, acid fuchsin methyl-green for metochondria, and various other stains used for the demonstration of protozoa and bacteria in tissues.

Tissues from all parts of the body of pellagrins were closely examined after being prepared according to these various special fixations and stains, but in no instance did I find any structure-organism or cell alteration that could be regarded as specific to pellagra.

PART III.—DISCUSSION.

When one compares the pathological alterations in pellagrous tissues with those changes seen in the various experimental animals, a striking similarity is observed (compare various summaries at the ends of the descriptions of each series with that of pellagra). Practically the same cellular changes are observed in: (1) the monkeys, white rats, Series I, and pigs whose diets consisted of food deficient in certain essential constituents, or whose tissues were unable to utilize the food substances in the circulation; (2) white rats, Series II, suffering from starvation consequent upon the total withholding of food; (3) rabbits fed on aluminum lactate, the presence of circulating toxins in the blood which interferes with nutrition; and (4) pellagrins. Of course slight variations are seen in the various individuals, but this can be readily explained by the fact that much variation always exists in the resisting powers of the various organs of individuals. No specific disease or abnormal process will cause identically the same pathological alterations in two individuals.

The cellular changes which were present in the tissues of both the animal series and pellagrins are:

(1) Passive congestion.
(2) Cloudy swelling.
(3) Hydropic degeneration.
(4) Fatty infiltration and degeneration.
(5) Hyalin degeneration.
(6) Amyloid infiltration.
(7) Pigmentation.
(8) Degeneration of nerve cells and axones.

There follows a brief general consideration of these various retrogressive changes—their nature and the etiological factors concerned in their production—with a view of applying them to the work in hand.

1. PASSIVE CONGESTION.

General passive congestion was the most common and striking feature of both series of tissues studied. Its general prevalence and wide distribution in the tissues both of pellagrins and of the experimental animals obviously demonstrate that no local conditions, such as intravascular obstruction or extravascular pressure, can be in any way responsible for it.

The causes of passive congestion, as is well known, are: (*a*) Cardiac affections, either weakness or valvular disease; (*b*) hindrance to normal respiration, such as accumulation of fluid within the thoracic cavity, intrathoracic newgrowths, or affections of the muscles of respiration, weakness or paralysis; (*c*) lowered blood pressure and pulse, this may be due to cardiac changes or to general inanition; (*d*) lack of general muscular activity; (*e*) general weakness and inanition. That most of these factors may be associated with malnutrition is well known.

With passive congestion other changes occur in the organs affected. The organ may become enlarged as a result of an increase of the blood, together with the associated edema and transudate, and a deep blue color is assumed. Oxygen in this blood is decreased. An increase of carbon dioxid occurs. Retrogressive changes soon manifest themselves, which are in the main due to: (*a*) Mechanical effects, stretching, and pressure; (*b*) chemical effects, diminished oxygen and carbon dioxid intoxication; (*c*) dimnished nutrition. Those organs drained by the portal circulation will show these retrogressive changes earlier and to a more pronounced degree, owing to an additional etiological factor—intestinal intoxication.

The effects of passive congestion upon an organ depend upon: (*a*) Its structure and function—whether highly specialized, whether the capillaries are well supported, the degree of vascularity; (*b*) its relation to the general venous system, such as the effects of gravity, hydrostatic pressure; (*c*) the degree, nature, and length of the stasis. If the capillaries are not well supported, hemorrhages may occur with pigmentation, as in the gastrointestinal tract. Concurrent with degeneration and atrophy of the parenchymatous tissue, fibrosis may occur. In extreme and prolonged passive congestion, necrosis and gangrene may be the final result.

Associated with this constant passive congestion in both the pellagrous and animal tissues, the heart in practically every instance showed retrogressive changes. One may ask whether these changes in this organ were primarily the cause of the congestion, or if the two conditions appeared concurrently as a result of inanition. The latter seems to be the case, as in no instance in the case of the animal series and only in exceptional cases in pellagrins were heart lesions present. Again no protophyte was found in any of the organs—pellagrins or animals—that could be responsible in any way for this extreme congestion.

Passive congestion as a consequence of inanition is the most plausible explanation of this phase of the pathological changes in both the pellagrin and animal series. Certainly this is true in the animal series, and as the pellagrous tissue simulated the former in practically every respect, one is justified in concluding that the passive congestion in pellagrins, together with the associated retrogressive changes, is due to nutritional disturbances.

Let us now consider some of the retrogressive changes that have been observed in connection with these tissues and see if they can be explained from the standpoint of malnutrition.

2. CLOUDY SWELLING.

Cloudy swelling is a term first applied by Virchow to the appearance of some organs—heart, liver, and kidney—after certain infections. The cut surfaces of these organs appear cloudy as if dipped in boiling water. Increase in size of organs, due to an increase of water within the cells, is often associated with this cloudy condition. The cloudiness is due to an increase of albuminous granules within the cells. Whether this increase is due to an accelerated absorption of albumin into the cells, resulting from stimulation of the latter by toxins, etc. (in which instance the cells have not utilized all the albumin), or is due to dissociated albumin already within the cell which makes up the cytoplasm, or to both conditions, has been a much mooted question. In fact the two processes are now fairly well recognized and can be differentiated. In both instances the granules clear up when fresh sections are placed in diluted acetic acid. When this is done in case of the former, the original or normal structure of the cell reappears. For example, if heart muscle is the site of cloudy swelling due to increase of albuminous granules as a result of increased absorption, the striations are seen again.

On the other hand, where granules are the result of disintegration of cytoplasm, while these also disappear in acetic acid, the original structure of the cell does not reappear, as this has been destroyed in the cytoplasmic disintegration. Thus, cloudy swelling, due to a superabundance of absorbed albuminous substance resulting from over stimulation of the cell—hence not in itself a cause of the death of the cell—is differentiated from granular disintegration of cytoplasm—a liquifaction necrosis, which has been described by Verworn (43), Durante (44), and others. The nuclear changes in true cloudy swelling are, as a rule, an initial increase of chromatin, which later accumulates in clumps and is followed by chromatolysis so that the nucleus is seen with difficulty. Owing to the great part that the nucleus plays in cell metabolism, changes in it are to be expected when the cell is over stimulated as is the case in cloudy swelling.

Probably no other cellular changes are more frequently described and oftener misinterpreted than cloudy swelling or albuminous degeneration. Every beginner in the study of pathology sees this condition in practically every section placed before him for study. The action of fixation fluids, Zenker's in particular, renders the cytoplasm of most parenchymatous cells granular in nature. Again, many cells are normally granular, such as leucocytes, tubules of the kidney, secretory glands, etc., and these granules are brought out more prominently as a result of certain fixitives. Post-mortem granular changes in the cytoplasm occur soon after death. So with all these conditions that may be responsible for the granular appearance of cells one can not be too conservative in the diagnosis of cloudy swelling from fixed sections.

True cloudy swelling is found in acute infection after certain poisons, such as phosphorus, may follow burns, and is found after starvation. Reference is made elsewhere to the cloudy swelling following starvation. It has been produced by Stilling (45) in the renal cells within 48 hours after ligation of the renal veins.

3. HYDROPIC DEGENERATION.

A plausible explanation of hydropic degeneration is that normally the constitution of protoplasm is in the form of colloid. As a consequence of disassociation of this colloid resulting from various factors, through cleavage or ionization, it forms crystalloid bodies. As long as the latter are present in the cell bodies in greater concentration than in the surrounding medium, water, of course, as a result of osmosis will flow into the cell. Attention has been called to the fact that in cloudy swelling the swelling of the tissue is due to an increase of water within the cell. This is probably the first step in hydropic degeneration. If sufficient water is thus imbided vacuoles may appear within the cell, as is the case with heart cells and nerve cells after certain acute infections.

4. FATTY DEGENERATION AND INFILTRATION.

The term fatty degeneration—based upon the idea that the fat found in certain cells undergoing morbid changes was derived from the proteid of the cell—is still used, although later investigations indicate that this fat has another origin. The expression used by Mallory (46) "Cell degeneration evidenced by the presence of fat" is a better term.

In the consideration of fatty changes in the cell, one must differentiate between fatty infiltration and fatty degeneration, although in some instances, as in the case of liver, this is impossible. The former, in all tissues except the liver, involves connective tissue cells; in the liver the parenchymatous cells are those affected. Fatty infiltration in certain connective tissues must be regarded as a normal process; for example, the accumulation of fat in subcutaneous tissues of some regions, in certain fascias—renal, omentum, and in the appendices epiploicae, etc. When it accumulates in other connective tissues which normally possess no fat, as in the heart, skeletal muscles, and connective tissue framework of the pancreas, the process may be regarded abnormal or pathological. Fatty infiltration of the liver may be both physiological, as in the later months of pregnancy or from overnutrition, or pathological as a result of disease. In fact it is impossible to state at all times whether demonstrable fat in the liver is physiological or pathological fatty infiltration or fatty degeneration.

Fatty infiltration is a storage of neutral fat within the cell. It results from an intake from the blood of more fat than the cell can utilize or from a reduction of the oxidation capacities of the cell so that it can not make use of that which normally should reach it. Of course, it is now generally accepted that neutral fats do not reach the cell from the blood as such, but that they enter in some altered form, perhaps in loose combination with globulin, and that later through the action of a cell ferment—lipase—neutral fats are formed. Some hold that the nucleus functions in this process, as demonstrable fat has been described in this structure during the process—Shattock (47).

Fatty degeneration, on the other hand, is primarily a cell degeneration. The nucleus undergoes chromotolysis and concurrently demonstrable globules of fat occur in the cytoplasm. That this fat has its origin from the degeneration proteid is a view that held favor for some time. This opinion was based upon a number of observations: (a) An actual increase of fat was observed in fatty degeneration of the liver even in starving animals. (b) F. Hoffmann (48) found more fat in the larvæ of flies grown from eggs nourished entirely on ox blood which contained a known amount of fat than the total fat contained in control eggs and the ox blood combined. (c) Again, there are the well-known experiments of Pettenkofer and Voigt (49) who found that upon feeding dogs a diet free from fat the carbon was retained in the form of fat. The explanation for the conversion of disintegrated proteid into fat is that the nitrogen-containing element is liberated while the carbon and its compounds are retained and converted into fat. Analysis of the urinary output seemed to confirm this view.

More recent work, however, goes to show that fat in fatty degeneration is not derived from proteid, but from preexisting fat. It has been shown in experimental phosphorus poisoning that while the fat in the liver increases there is diminution of fat elsewhere in the body. Taylor (50), Rosenfeld (51), and others have demonstrated this. Rosenfeld has shown that if a dog is poisoned with phosphorus or phloridizin and then fed with a foreign fat, such as mutton tallow, which differs in composition from dog fat, the fat in the degenerated liver approximates in composition that of the tallow.

According to this later view, then, fat in fatty degeneration has its origin from preexisting fat, which may be transposed from other cells or derived from masked fat already within the cell. That fatty degeneration may be preceded and accompanied by myelinic degeneration seems very probable—Kaiserling and Orgler (52), Lohlein (53), and others. Glycogen may contribute to the formation of this fat.

Fatty degeneration follows cloudy swelling of the cell; hence may be regarded as a second stage in cell degeneration. Those causations responsible for cloudy swelling, therefore, may be responsible for fatty degeneration. Other etiological factors are acute nonbacterial affections which include various poisons—arsenic, antimony, phloridzin, etc. It occurs in malnutrition, such as anemia, chlorosis, cachexia, starvation. It may be a physiological process as well, as in the normal secretion of the mammary and sebaceous glands.

5. HYALIN DEGENERATION.

Frequently in various cell degeneration materials accumulate either within the cell or in the intercellular spaces, which appear translucent or glossy. Various terms have been applied to this substance, depending upon its consistency, color, and chemical reaction.

Generally, if it is colorless, firm, and stains deeply with basic dyes, it is called hyalin. Substances that are colorless, firm, and react to iodin or stain metachromatically with methyl-violet are spoken of as amyloid. If instead of being firm, the substance is in the nature of a fluid and is colorless, the term mucin or mucoid is applied to it, while if the material is semisolid and yellowish or yellowish brown in color, it is referred to as colloid.

It is only with hyalin and amyloid changes that we are concerned, as these are the changes occasionally observed in the tissues of both the experimental animals and the pellagrins. Regarding the substance generally considered as hyalin, it may be stated that it occurs in various tissues and under different conditions. Sometimes it is found in thrombi and is known here as hematogenous hyalin, because it is derived from the blood elements—red blood cells as a result of agglutination or disintegration, or from the platelets. It may appear in the urine as clear translucent bodies, spheroids or cylinders—whether this is derived from the epithelial elements of the tubules or from blood structures is a mooted question. Hyalin is also formed in the connective tissues of the heart, lymph glands, and arteries; in the capillaries of the brain, liver, kidneys, spleen, thyroid, pancreas, and prostate: and in the connective tissue new growths of syphilis and tuberculosis. Occasionally it is found as an intracellular deposit in plasma cells, cancer cells, Russell's fuchsin bodies, smooth muscle fibers, and Zenker's degeneration of striated muscle.

The etiological factors in the production of hyalin are chronic inflammations such as tuberculosis, prolonged pyogenic infections, typhoid fever, smallpox, trichinosis, etc., and after nonbacterial toxins, alcohol. It also appears apparently without any decided causes.

6. AMYLOID INFILTRATION.

Amyloid infiltration, or a better term is chondroid infiltration, for amyloid is now regarded as a combination of a proteid, histon, and chondroitin sulphuric acid, thus similar to cartilage in composition, is found in the connective tissue framework of various organs. For example, in amyloidosis of the liver, the substance is first found in the capillaries just outside of the endothelial layer. Later it is seen to accumulate in the connective tissue of the arteries, and finally may be seen in the veins. Amyloidosis may be either general or local. In the former condition, amyloid usually makes its appearance in the spleen, liver, and kidneys. Occasionally it is seen in the skin, bones, lung, and nervous tissue. It is doubtful whether it ever appears as an intracellular deposit. Among the causes of amyloid infiltration may be named prolonged suppuration with breaking down of proteids; i. e., tuberculosis, syphilis, chronic suppurative osteomyelitis, actinomycosis, chronic dysentary, ulcerating new growths. It is also found in malaria eachexia, chronic anemia, and leukemia.

Thus it is seen that both hyalin and amyloid changes may result from many factors.

From this general consideration of retrogressive changes it is seen that cloudy swelling, hydropic degeneration, fatty infiltration and degeneration, hyalin degeneration, and amyloid infiltration may result from disturbances in nutrition. For example, cloudy swelling has been shown to develop after ligation—passive congestion—of the renal veins. It is also generally seen in tissues after prolonged starvation. Hydropic degeneration is a sequence of cloudy swelling. Fatty infiltration, whether due to defective oxidation, a condition which may be associated with passive congestion, or to the storage of neutral fats within the cells, is associated with malnutrition. Fatty degeneration which may be a sequence to cloudy swelling—a second stage in the retrogressive changes is frequently found in starvation. Its presence in anemia, chlorosis, and cachexia is further evidence of its association with nutritive disturbances. Our series of animals show that both hyalin and amyloid changes may be present in malnutrition. Also, these changes have been observed in post-mortem examinations where death has resulted from extreme inanition and where no evidences have been found that chronic suppuration processes have been present.

Thus from the observations of others as well as from our own we may conclude (1) that retrogressive changes do frequently occur as the result of extreme nutritional disturbances, (2) that the cellular changes are practically similar whether the malnutration is due to withholding of food, inability of the tissues to utilize food that is present in the circulation, absence of some essential constituent of the food, or toxins which may interfere with assimilation; (3) that the cellular alterations in pellagra are practically identical to those obtained in our experimental animal series as a result of induced nutritional disturbances and consequently all cellular changes in pellagra may be explained from the standpoint of malnutrition.

7. NUTRITIONAL DISTURBANCES.

Before considering these various pathological conditions, a brief discussion of nutritional disturbances will not be out of place.

Nutritional disturbances are due to the following factors: (1) Insufficient food, either by withholding it or due to gastrointestinal disturbances—starvation in varying degrees; (2) foods in sufficient quantities but in such condition that the assimilation organs can not use them as foods; (3) constitutional defects in the organism, so that foods, even in ideal combinations for normal metabolism, can not be utilized; (4) foods deficient in some essential constituents—vitamines.

With the symptoms and pathology of starvation we are familiar. Circulating proteins are first drawn upon. This is followed by a withdrawal of the glycogen from the liver and muscles in general. Then the fatty stores of the body follow. The next step is a shrinkage in the muscles—those least used are first to show this condition, while those most active undergo diminution last, as, for example, the heart. Excretions of all organs are diminished. The leucocytes are reduced. Death follows.

A number of disorders are due to foods taken into the body which, although sufficient in amount, are nonassimilable. Scurvy is a typical example of this and may be due to either a deficient amount of proteids, as in the case of those whose dietary consists chiefly of potatoes, or when proteids are present in superabundance. In the latter condition, it is generally canned or salted meats that produce scurvy. Barlow's disease in infants, much similar in symptoms to the scurvy of adults, is usually found in those whose food—milk—has been artificially prepared. Both diseases are rapidly ameliorable to correction of diet. In case of scurvy, fresh fruit or acid fruit juices, and in case of Barlow's disease, nontreated, natural milk, are sufficient to correct these disorders. In both diseases the food was altered in some way so that sufficient assimilation could not take place. Whether the alteration is due to some association or dissociation of the salts—calcium, phosphorous, sodium—so that they can not be utilized, or is due to some other change in the food devitalized, still remains a debatable problem.

That mineral matter is essential to metabolism has long since been known. Deficient iron causes disturbances in the hemopoietic organs. Insufficient calcium in foods results in inadequate growth of bones. While phosporus incommensurate to the body's needs results in delayed growth.

On the other hand, that there is a destruction or alteration of some substance in the food—a devitalization—appears probable. The term "vitamine" has been applied to this substance. Regarding this term, Stewart (54) comments: "It might be better in the present state of our knowledge to avoid giving those bodies a name which may easily mislead. They might possibly be provisionally spoken of as vitines, a term involving no assumption as to their chemical nature, and implying only their importance in the nutritional processes associated with the life (and growth) of the tissues." The chemical structure of vitamines (vitines) is problematical—probably a basic nitrogenous substance. That it can be extracted from foods rich in nucleo-proteids has been shown by Funk (55) and McKay, and its nature has been an important problem for study in the Hygienic Laboratory.

Many now hold that scurvy is due to deficiency of vitamine, and in this same category of diseases rickets, pellagra, and beriberi are included. That the last is sometimes due to a dietary of polished rice is no longer questioned. The vitamine of rice is contained within the outer coats and in the milling of rice these are removed. Peripheral neuritis, characteristic of beriberi, has been caused in pigeons by feeding them polished rice. The pathological changes in these pigeons include, in addition to those changes that accompany neuritis, complete atrophy of the thymus, disturbances of the pituitary, and atrophic changes in the sex glands.

Regarding the other pathological changes consequent upon the lack of nutrition, Adami (56) states: "Beyond simple shrinkage there are no marked changes until the animal has lost 10 per cent of its weight, then cloudy and granular alterations are to be seen in the cells of larger glands—liver and kidney—and in the muscle fibers. In the liver cells, according to Statkewitsch, the glycogen disappears at a comparatively early stage, and there is cloudy swelling; later, again, in the outer cells of the lobules, there is extensive fatty infiltration; large fat globules distending the cells. In the mucous cells of the salivary glands there are the appearances of fatty degeneration."

Thus it is seen that according to the observations of others, nutritional disturbances are associated with cellular disturbances similar to those observed by us. Space will not permit a general comparison of tissue changes in pellagra with those of beriberi, rickets, and scurvy—but there is much in common. In fact from the pathological standpoint, I can see no reason why pellagra can not be included in this category. Likewise there can be no objection to including within this class the monkeys, white rats, Series I, and pigs whose diets while quantitatively sufficient certainly consisted of foods deficient in some essential constituent. The cellular alterations in all are very similar.

8. PATHOLOGICAL ALTERATIONS IN THE NERVOUS SYSTEM.

The pathologic retrogressive changes in the cells of the nervous system are demonstrated in the following: (1) Swollen cell body; (2) chromatolysis; (3) peripherally located nucleus; (4) vacuoles, fat, and pigment in the cytoplasm; (5) disappearance of axonal medullary sheaths; (6) complete necrosis and disappearance of cells. These retrogressive changes have many etiological factors which may be classified as follows: (*a*) Constitutional—anemia, cachexia, chlorosis; (*b*) mechanical trauma; (*c*) circulatory disturbances—thrombi, emboli, endarteritis, hemorrhage; (*d*) toxins—bacterial, mineral chemical, and vegetable; (*e*) heredity—transmissible defects.

Just how the nervous system is affected is by no means a settled question. For example, many hold that there is a certain specificity between circulating toxins and nerve cells. Thus Oppenheim attributes tabes to this selection. Marie, on the other hand, held the opinion that this disease was due to syphilitic lesions involving the pericellular lymphatics of the nervous system.

A very feasible explanation of nerve cell degeneration is the so-called exhaustion theory of Edinger's based upon Weigert and Rous's theory of cell equilibrium. The theory is, in substance, this: All cells making up an organism are normally in a stage of equilibrium. Cells normally restrain other cells from excessive growth. However, if one cell or group of cells is destroyed, neighboring cells by hyperplasia fill the space originally occupied by the destroyed cells. Again, if a group of cells become weak and lose their resistance power, other surrounding cells may proliferate even to the complete destruction of the weak cells. Thus cirrhosis of the liver is simply a primary weakening, a loss of resistance, a degeneration of the parenchymatous tissue, accompanied by an overgrowth of more resistant cells—interstitial connective tissue cells.

Applied to the nervous system, the process is as follows: The nerve cell loses its resistance as a result of various factors. This may be due to insufficient nutrition; it may be due to the fact that the nerve cells are congenitally impaired; or it may be due to excessive function demanded of the nerve cell combined with nutritional disturbances. At any rate, when the cell is so impaired that it loses its normal resistance, proliferation of the glial cells occurs. The energy of growth of the latter cells may be sufficient to cause the other functioning cells to degenerate. In fact, in many lesions of the nervous system it is difficult to state whether the lesion is due primarily to a degeneration of nerve fibers followed by gliosis or that the latter was responsible for the degeneration of the nerve fibers.

It seems that this exhaustion theory is the most logical one in interpreting the factors concerned with many nerve degenerations. Based on the general functioning demands made upon the nerve cells, those groups likely to suffer most from exhaustion are: The reflex arch fibers, sensory more so than the motor, and the pyramidal tract. The peripheral neurones would suffer before the central and perhaps the projection tracts before the association tracts. The arch reflexes and pyramidal tracts, of all others, function most in the normal activities of life. Hence, it would be these tracts that would first show the results of exhaustion, especially where malnutrition is concerned, such as seen in anemia, cachexia, and intoxication.

One of the most frequent sites of degeneration is seen in the posterior tract—columns of Goll and Burdach. It is seen in locomotor ataxia, chronic ergotism, pellagra, and many intoxications. The motor neurone of the arch is involved in many disorders, such as anterior poliomyelitis, both acute and chronic, progressive spinal muscular atrophy, progressive bulbar atrophy, etc. The pyramidal tract, together with the anterior horn cells, are destroyed in amyotrophic lateral sclerosis. Very frequently, however, both the reflex arch fibers and the pyramidal tract are simultaneously involved as in posterior lateral sclerosis; Friedreich's ataxia; constitutional disturbances, such as anemia and pellagra; and in chronic poisoning due to certain metals, such as aluminum—Siem (57), Von Doelken (58); lead—Stieglitz (59); mercury—Tirelli (60); and other substances—Tschisch (61).

It may be that the reflex arch as manifested in the degeneration of the posterior tract is first involved because of its greater functioning activity in many of these combined degenerations and scleroses, and that the pyramidal tract is later implicated. That this may be true in pellagra is very likely, which would account for the fact that many have described degeneration in the posterior tract, others in the pyramidal tract, and still others have noted both tracts involved. I have observed sections from pellagrous cords in which the posterior tract alone was involved and others in which both the lateral and posterior tracts were degenerated. In general we may assume, then, that under average conditions the posterior tracts first show retrogressive changes in pellagra and malnutritions in general and that the pyramidal tract may follow in this course. If the retrogressive changes are prolonged, other groups of cells may be included, such as Clark's column—Babes (62). Exceptions to this rule will be found, of course, in the numerous examples of inherited deficiencies of certain cells and tracts, in which case these will be the first to be involved.

It appears, then, that degeneration of certain tracts in the spinal cord in pellagra is not necessarily due to any affinity between a specific toxin of pellagra and certain nerve cell groups, but, on the other hand, the retrogressive changes may be due to disturbed nutrition as a consequence of this disease. Similar nutritional disturbances may be seen in certain constitutional disorders, as in anemia, cachexia, and chlorosis. They may result from numerous toxins, bacterial, vegetable, chemical, and mineral. All of which may produce similar pathological alterations in the nervous system.

Further, Prof. Voegtlin's feeding experiments demonstrate that similar alterations may occur in the absence of certain essential elements in the food. It will be recalled that in spinal cords of Monkey II and VIII, Burdach's columns in both were degenerated, while a more or less diffuse degeneration was present in the dorsal region. In other animals the spinal cord contained many alterations that could not be differentiated from those seen in pellagrins, with the exception of excessive pigmentation described in the latter by numerous observers. I did not note any marked pigmentation in the nerve cells of these animals, nor did I observe unusual pigmentation in pellagrous nerve tissue.

From a pathological standpoint, then, cellular alterations in the spinal cord as seen in pellagra are not specific to this disease but are seen in many types of malnutrition and may be produced experimentally by altered and insufficient feeding.

In the brain it is the pyramidal motor cells that are most frequently involved in pellagra, and the exhaustion theory is equally applicable to the explanation of the morbid changes found here. Next to the reflex arch, as has already been indicated, the pyramidal tract exercises the greatest function in the normal activities of life, and, according to the exhaustion theory, retrogressive changes in the central motor neurones would early present themselves when the nervous system is involved. Reference has already been made to Meyer's "central neuritis," found in patients dying from exhaustion, in which typical retrogressive changes were found in the perikaryons of the pyramidal nerve tracts. Meyer held that the etiological factors concerned in the production of this condition were of a toxic nature—alcohol. Wilgus concludes that the changes found in the cells of the pyramidal tracts in pellagra are similar to those described by Meyer, hence a central neuritis.

While my observations on central motor cell alterations in pellagra are limited, they have been sufficient, I feel, to warrant me in confirming Wilgus's conclusions. Involvement of the central motor neurone in pellagra, then, is no manifestation of a specificity of this disease for these nerve cells, but, on the other hand, it shows that these cells have lost their resistance—exhaustion—in the process of the disease.

Our series of experimental animals show identically the same changes described by Meyer in Betz's cells. It will be recalled that these changes were produced by malnutrition, either to the absence of some essential constituent in the food or to total absence of food or to intoxication (aluminum lactate) which may be a nutritional disturbance.

Pathological alterations in pellagra in the central nervous system, then, can be explained from the standpoint of nutritional disturbances.

At this point it will be well to state that one can not emphasize too much the error that many have fallen into regarding the presumed determination of the etiological factors of pellagra as a result of certain pathological changes obtained from the administration of certain substances, such as aluminates, silicates, etc. Cell alterations in the nervous system of pellagrins, as well as in the other organs of the body, are not specific to this disease. As has already been pointed out, they may result from other factors, most notably malnutrition, which perhaps in the final analysis alone may be responsible.

9. PIGMENTATION.

One other subject, pigmentation, demands a brief general consideration before our final conclusions are submitted. Its presence, especially in the nerve cells of pellagrins, has been described by many observers. Some hold that its presence in nerve cells is characteristic of pellagra, although the nature of the pigment is not stated.

The endogenous pigments derived from the blood—hemoglobin—and certain autogenous pigments which accumulate in some cells—heart and nerve cells—in later life, chief of which is lipochrome, are the ones with which we have to deal.

Hemosiderin is a collective term for an amorphous yellow or brown pigment derived from hemoglobin. It differs from the other derivative of the latter, which is known as hematoidin, in that it contains iron in loose combination—thus differing in this respect also from hemoglobin, its antecedent—which contains iron in close or masked combination with proteid. It is this iron, which can be readily detected microchemically, that characterizes hemosiderin. With ammonium sulphide it forms a black precipitate—iron sulphide, Quincke's test. The ordinary test used, however, is that known as Perl's test; with potassium ferrocyanide and dilute hydrochloric acid an insoluble Prussian blue is formed. Hemoglobin, on the other hand, while it contains iron, does not react with these tests, owing to the fact that the iron is masked or closely bound with the albumin.

Hemosiderin is a product of the vital activity of cells and consequently is an ante mortem product, while precipitates of hemoglobin are usually due to post-mortem changes or to the action of certain fixation fluids—formalin. Hemosiderin is found in the outer zones of hemorrhagic areas, either free or within certain cells, such as leucocytes and endothelial cells. It is found in organs as a result of hemorrhages into them, or after extensive degeneration of red blood cells. The spleen, liver, pancreas, lymph glands, and walls of intestines are frequently sites of hemosiderin. The liver cells contain this pigment in cases of pernicious anemia and hemochromatosis.

Von Recklinghausen first called attention to the latter. Deposits of this pigment, according to him, are found in the intestinal wall which assume a yellow or yellowish brown color. When disease is more advanced, cirrhosis of the liver and pancreas occurs with depositon of hemosiderin within these organs. Diabetes may be present—diabetes bronze of the French. According to Dr. Maude Abbott, hemosiderin is found in the majority of cirrhotic livers. Hence the presence of this pigment is not specific to any particular disease, as is believed by some. Some hold that hemochromatosis is due to a mild infection, as an acute type of hemochromatosis has been described; i. e., a bacterial cyanosis due to B. coli bacteriemia.

In tissues described from the experimental series, it will be recalled that much hemosiderin was frequently found in the spleen and occasionally in other organs, liver and kidneys, thus indicating that an excessive destruction of red blood cells was taking place during life. Hemoglobin and hemosiderin were the only endogenous pigments of any degree that could be identified. In some animals, only traces of pigment were found in and surrounding nerve cells of both the anterior horn cells and pyramidal cells of the cortex. The nature of this was not determined, although it simulated lipochrome.

From references given it will be seen that pigmentation of anterior horn cells and spinal and sympathetic ganglia cells was almost a constant finding with many observers. While the nature of this pigment is not discussed, it is in all likelihood lipochrome. I did not find this to be the case in my examinations of nerve tissues taken from pellagrins. No extreme pigmentation of nerve cells was seen. Lipochrome was present, however, in various amounts. This pigment is not by any means specific to pellagra, but collects with advancing years, in addition to nerve cells, in various organs such as the heart, liver, adrenal, smooth muscle of intestine, and seminal vesicle. Marchi also held that nerve cell pigmentation is not specific to pellagra.

In all likelihood this pigmentation of nerve cells as found in pellagrins is accelerated as a consequence of the degeneration process going on in the nervous system, but the pigmentation must not be regarded as a condition specific to pellagra.

CONCLUSIONS.

1. The morbid tissue changes resulting from malnutrition, as shown in our animal series, are (*a*) passive congestion in practically all tissues; (*b*) various degrees of retrogressive changes in many of the thoracic and abdominal viscera such as cloudy swelling, hydropic degeneration, fatty infiltration and degeneration, hyalin degeneration, amyloid degeneration; congestion, hemorrhage and ulceration of gastrointestinal tract: (*c*) pigmentation chief of which is hemosiderin; (*d*) degeneration in the central nervous system consisting chiefly of the reflex arches and the pyramidal nerve tracts.

2. The tissue alterations, including the degenerative changes in the nervous system, occurring in our series of animals as a result of malnutrition are strikingly similar to those observed in pellagrous tissue.

3. From a pathological standpoint there can be no objection to the classification of pellagra along with rickets, scurvy, and beriberi as dietary diseases.

4. A most rigid examination of numerous tissues obtained from pellagrins revealed no microorganism that can be regarded as a specific etiological factor, nor were any cell alterations present that can be considered as specific to the disease.

5. Pellagra, then, possesses no characteristic cell alterations, but the pathological changes are those resulting from malnutrition. Consequently it is erroneous to assume that certain substances such as silicates, aluminates, etc., are the etiological factors of pellagra, as some have done, because of the pathological changes that have been induced as a result of the administration of these substances.

6. The degenerations that occurred in the nervous system both of our series of animals and in pellagrins are readily explained by the exhaustion theory of Edinger, Meyers, and others.

7. The pathological changes in tissues in malnutrition are very similar, whether resulting from (*a*) no food; (*b*) unbalanced diets; (c) mild circulating toxins which interfere with nutrition of cells. In (*a*) congestion and fatty degeneration were more pronounced, while in (*b*) more pigment—hemosiderin—was present.

To Dr. John F. Anderson, formerly Director of the Hygienic Laboratory, and Prof. Carl Voegtlin, the writer is especially indebted for many suggestions. Appreciation is also due to Technical Assistant Walker D. Cannon, for valuable assistance rendered in the translation of that literature relative to pellagra.

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EXPLANATION OF PLATES.

The illustrations are microphotographs of sections taken from various organs in the experimental animal series. Unless otherwise indicated, the sections were stained in hæmatoxylin and eosin.

Fig. 1. Monkey I: Spinal cord, cervical region, Pal Weigerts. Degeneration of the column of Burdach is marked.

Fig. 2. Monkey I: Spinal cord, dorsal region, Pal Weigerts. A diffuse unilateral marginal degeneration of all tracts is seen.

Fig. 3. Monkey I: Spleen, showing amyloidosis of the Malpighian nodules. The pulp is intensely congested. a. Amyloid in Malpighian areas.

Fig. 4. Monkey I: Ileum. This section shows: a. Erosion of superficial epithelium. b. Congestion of submucosa. c. Atrophic muscular layer; in some places it has almost disappeared.

Fig. 5. Monkey II: Liver. The lobules as well as the cell cords are broken up as a result of congestion and cirrhosis.

Fig. 6. Monkey IV: Liver. Portal vessels and intralobular capillaries are markedly congested. The cell cords are broken up into irregular islets.

Fig. 7. Monkey V: Small intestine. Beginning ulcer formation. a. Necrotic mass, consisting of an amorphous granular substance and fibrin. b. Area of cellular infiltration—polymorphonuclear leucocytes, erythrocytes, fibrin, plasma cells, and new connective tissue cells are seen in this area. c. Intensely congested submucosa; the entire mucosa is congested and inflamed; only the fundi of the crypts are seen.

Fig. 8. Monkey VI: Stomach. This section shows an ulcerous area of the mucosa; the surrounding mucosa is intensely congested and hemorhagic. a. Necrotic substance and fibrin.

Fig. 9. Monkey VII: Heart. The muscle cells of the myocardium are vacuolated. Transverse striations are absent and sarcoplasm not affected by the vacuoles is granular.

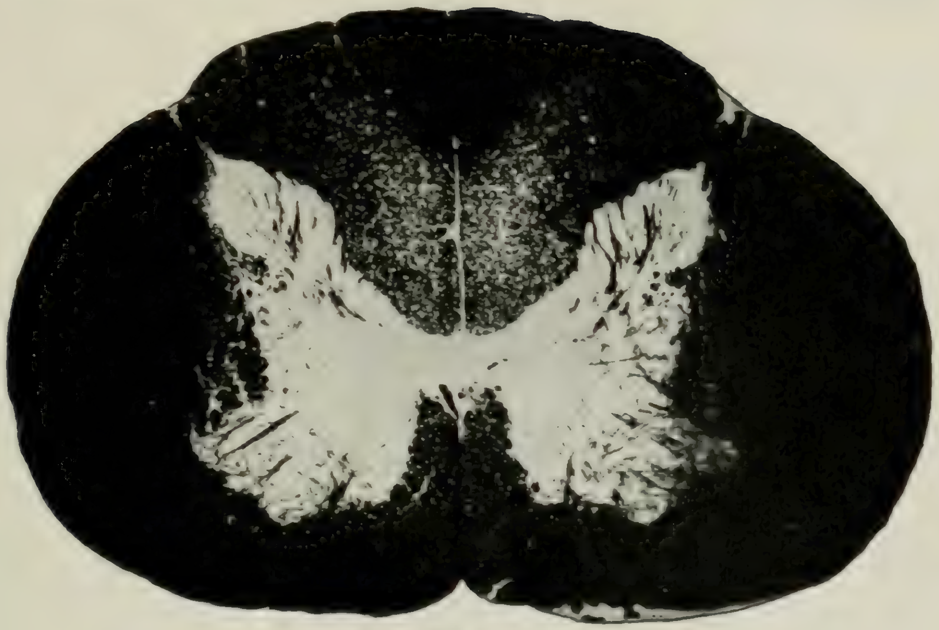
Fig. 10. Rat I, Series I: Spleen. Unstained section after treating with potassium ferrocyanide and hydrochloric acid—Perl's test. a. Malpighian follicles unstained. b. Deep blue granules of hemosiderin.

Fig. 11. Monkey VIII: Cord, cervical region, showing degeneration in the column of Burdach. The negative of this photograph was retouched at the anatomical margin of the column. A mild diffuse degeneration is seen in the ground bundles of the anterior and lateral tracts. Technique, Pal Weigert's method.

Fig. 12. Monkey VII: Cord, dorsal region. In this section many fibers in the column of Goll are degenerated. A diffuse degeneration and sclerosis is seen throughout the white matter. The central canal is dilated. Technique, Pal Weigert's method.

Fig. 13. Monkey IV: Cerebrum. This section shows a large pyramidal cell with nucleus eccentrically placed. No Nissl's granules were present. Small vacuoles are seen in the cytoplasm. Technique, alcohol fixation, methylen blue.

Fig. 14. Monkey IX: Spinal cord, anterior horn motor cells. The cells are swollen; no Nissl's granules are present. Technique, alcohol fixation, methylen blue.



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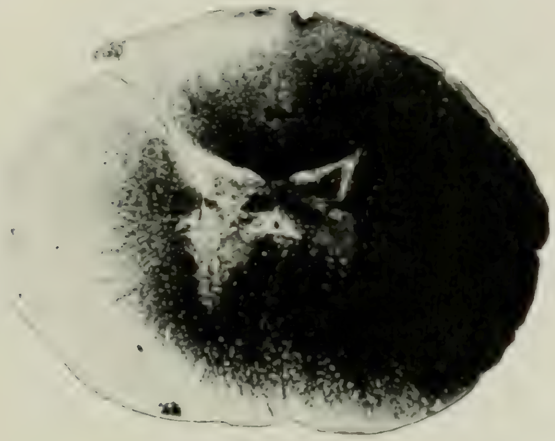

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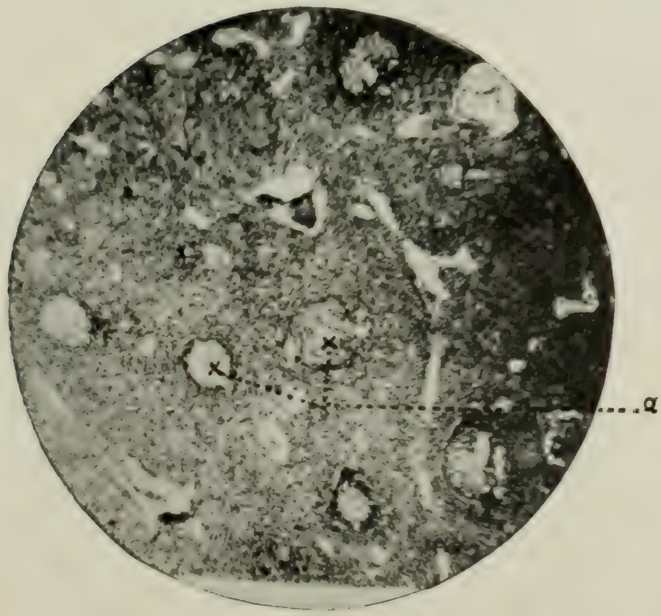

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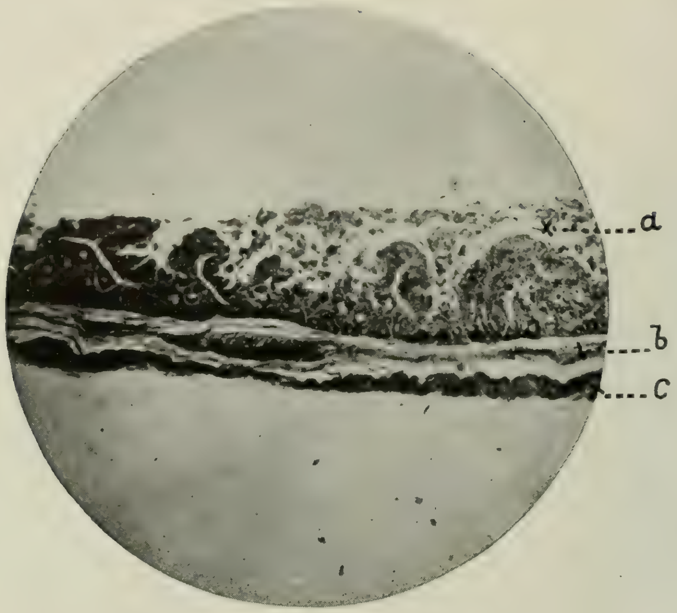

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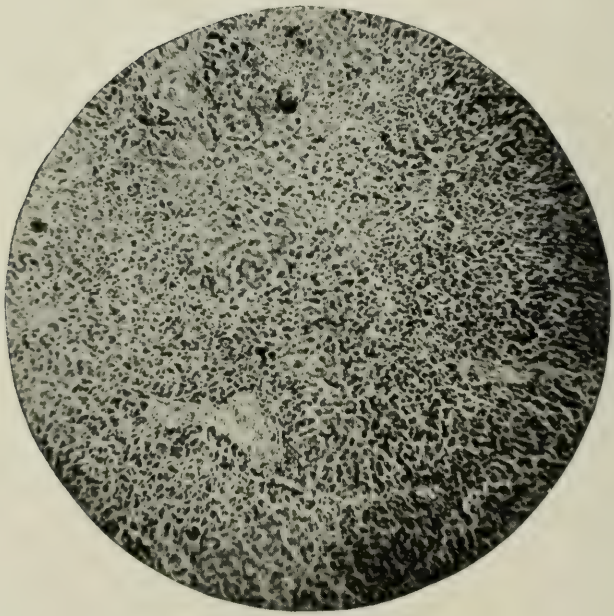

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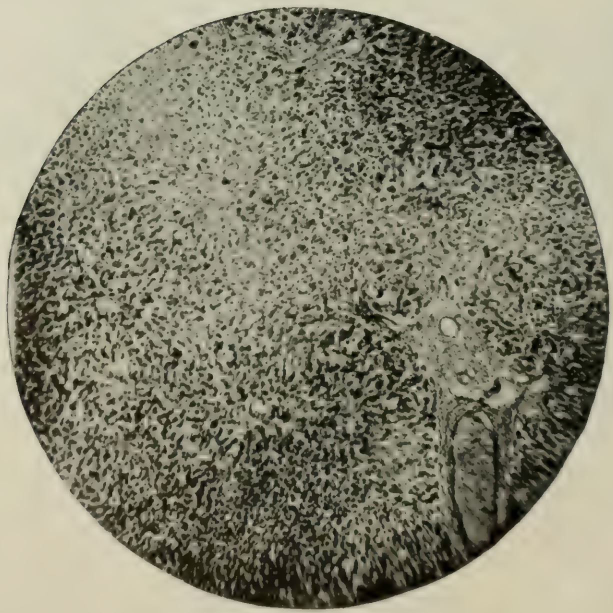

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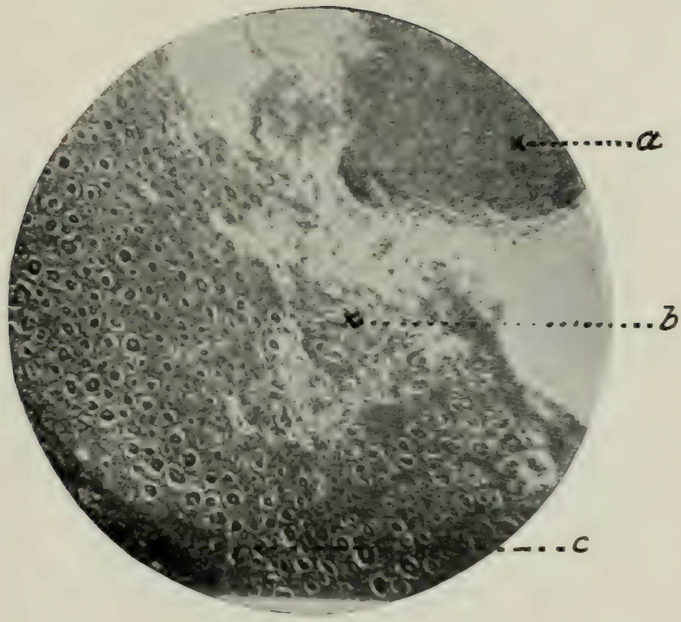

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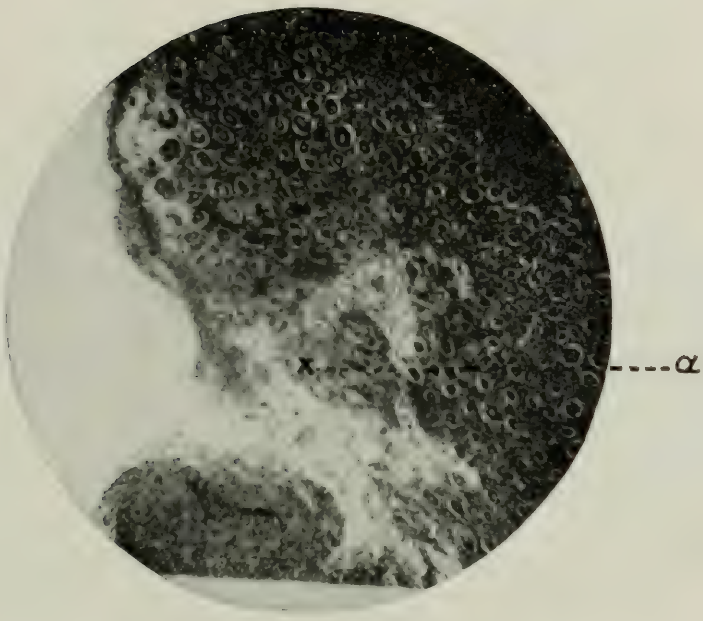

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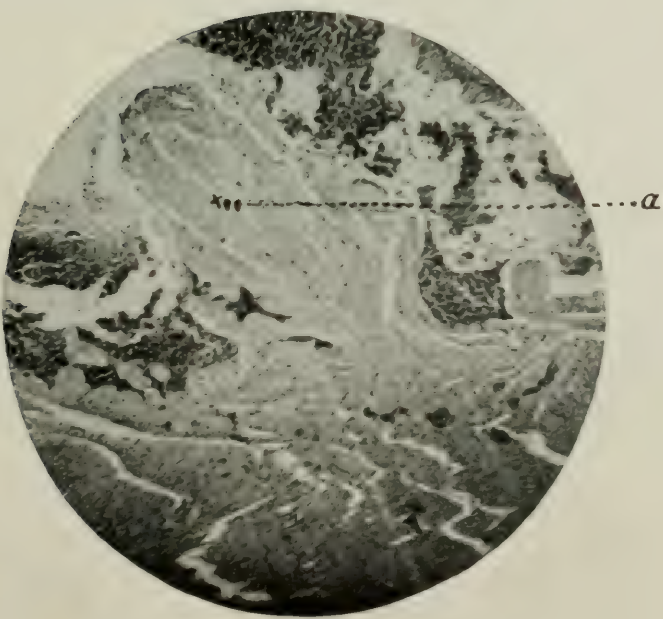

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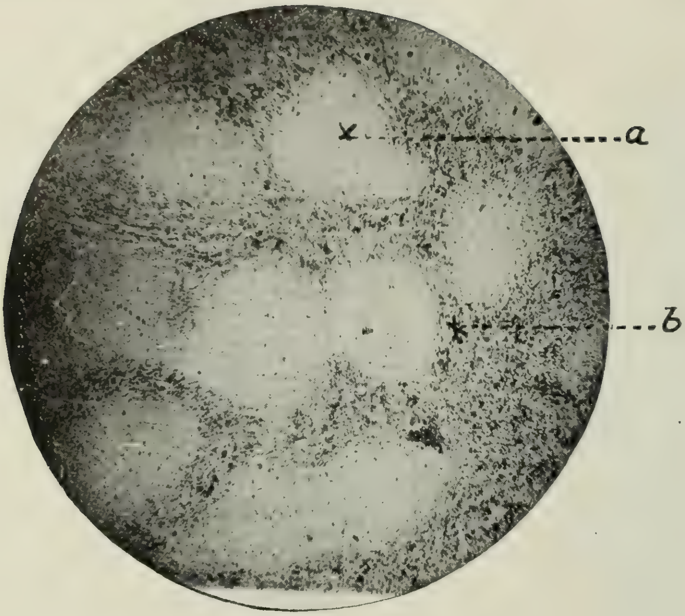

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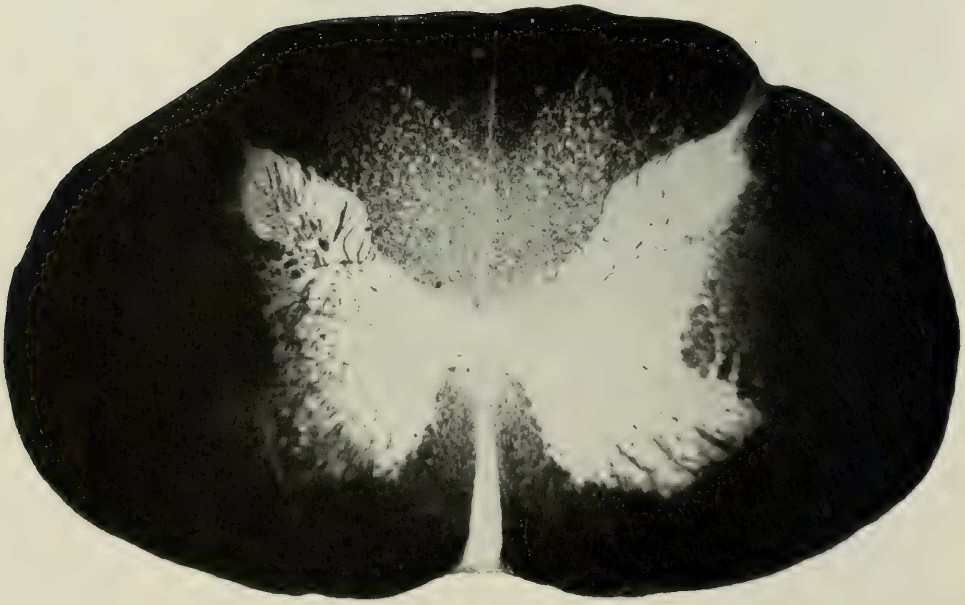

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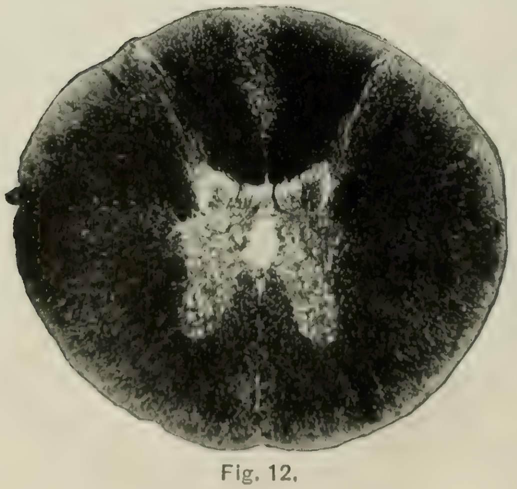

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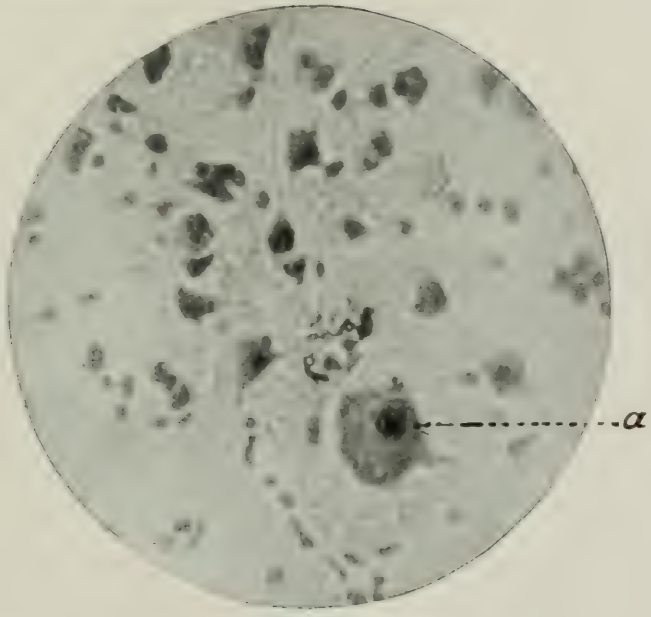

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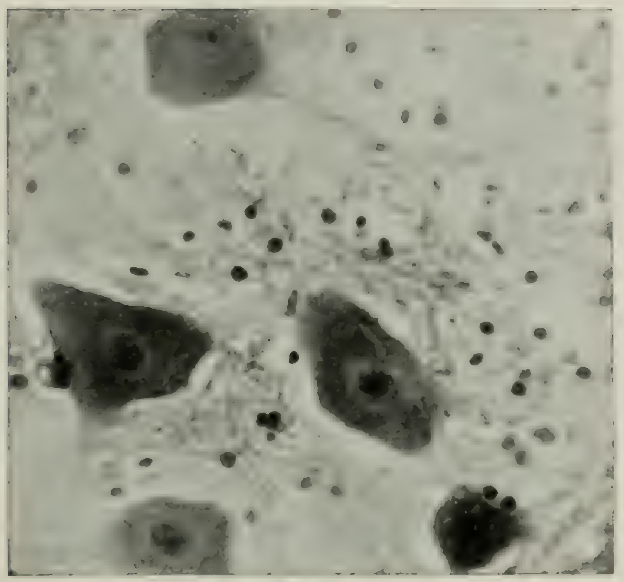

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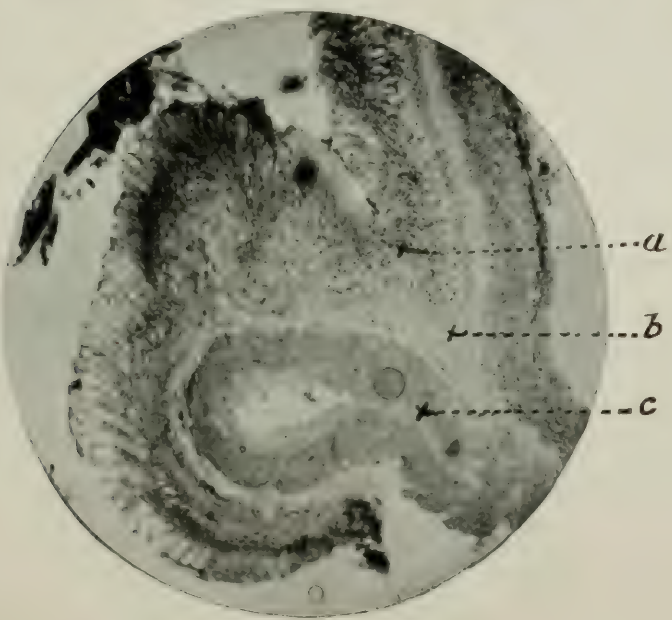

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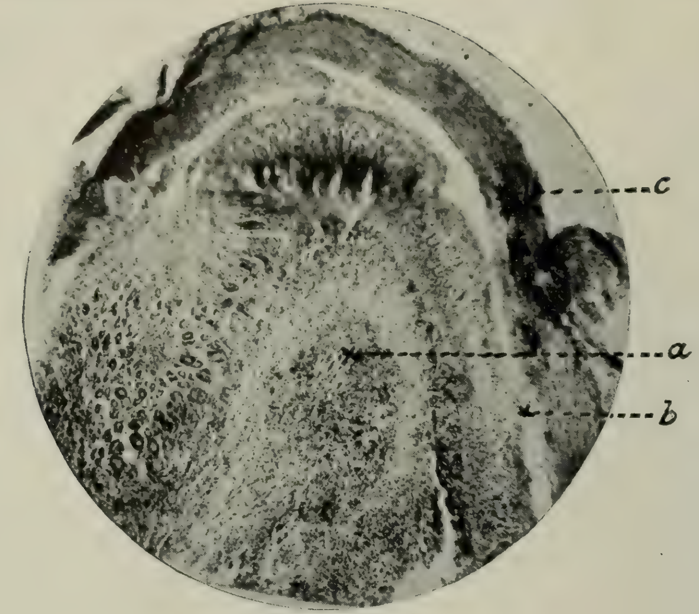

Fig. 16.

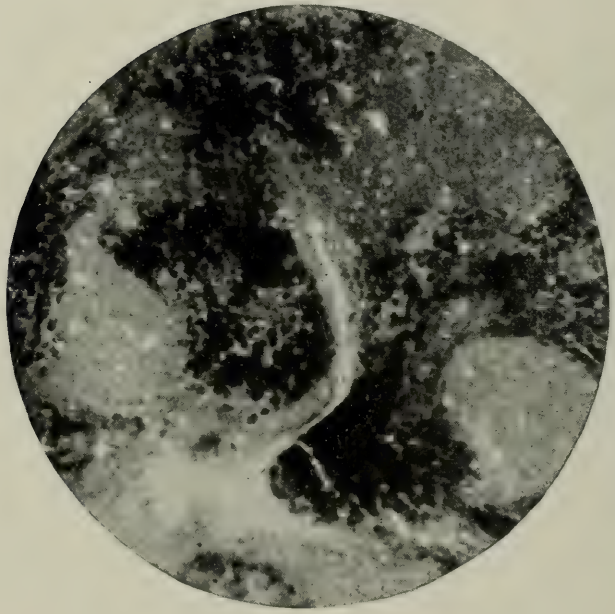

Fig. 17.

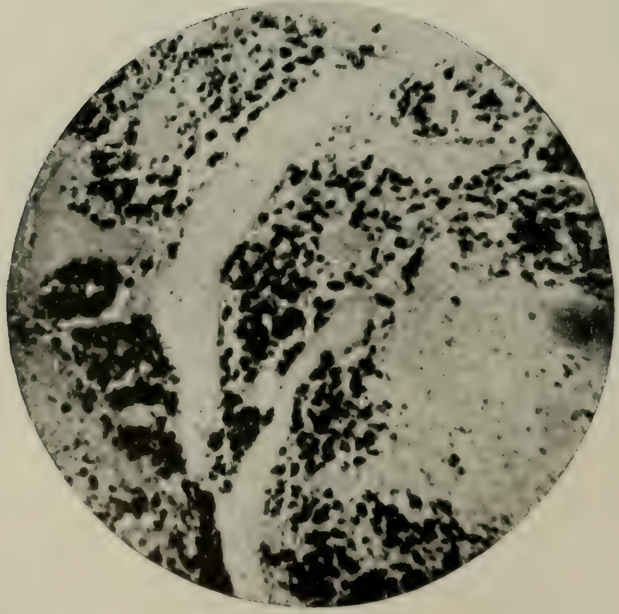

Fig. 18.

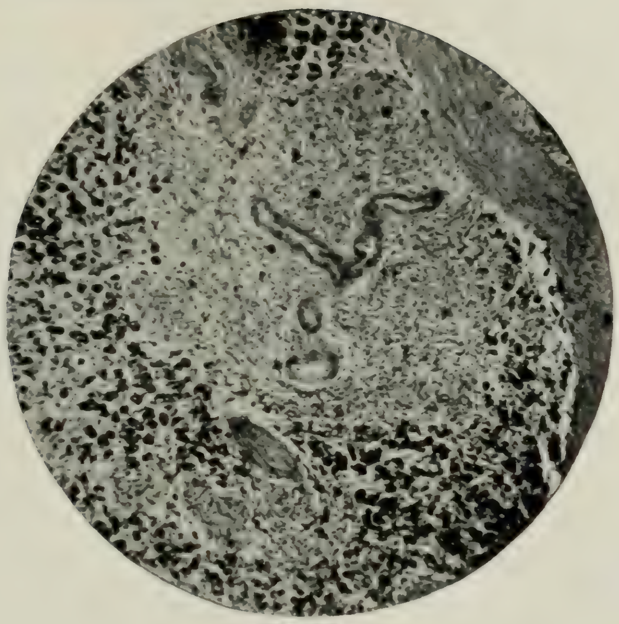

Fig. 19.

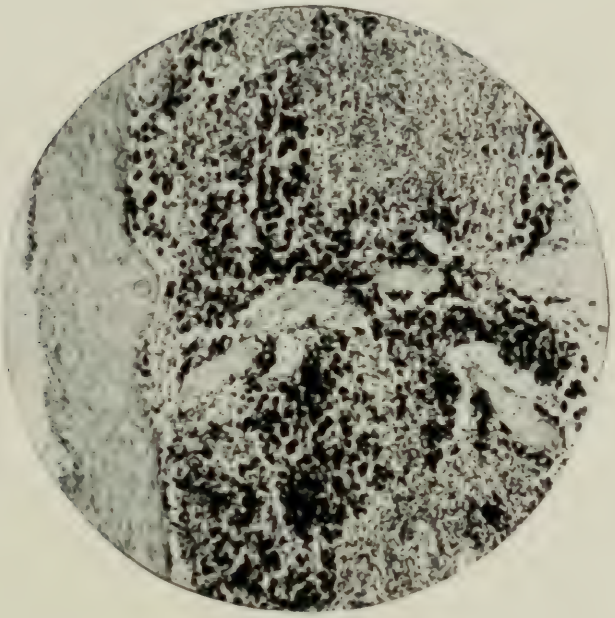

Fig. 20.

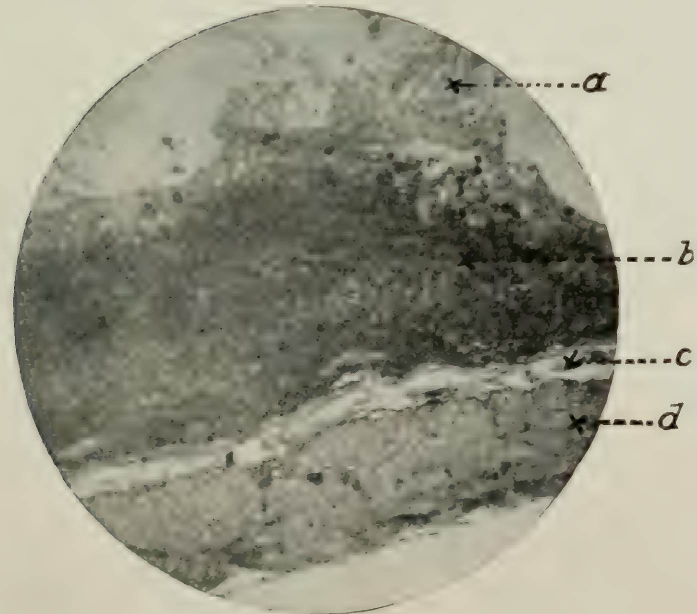

Fig. 21.

Fig. 15. Rat III, Series II: Stomach. This section shows the extensive changes that occur in starvation. All the epithelial cells of both the surface and gland crypts have disappeared. a. Plugs of mucin are seen between the connective tissue crypts. b. Submucosa and c. muscularis mucosae are necrotic.

Fig. 16. Rat III, Series II: Stomach, showing ulcer: a. Area of ulcer. b. Submucosa. c. Muscularis mucosae.

Fig. 17. Pig I: Spleen. Zenker's fixation—hæmatoxylin and eosin, showing extreme congestion and pigmentation.

Fig. 18. Pig I: Spleen. Unstained section after treating with potassium ferrocyanide and hydrochloric acid, Perl's test. The hemosiderin stands out prominently.

Fig. 19. Pig III: Spleen. Zenker's fixation, hæmatoxylin and eosin, showing extreme congestion and pigmentation.

Fig. 20. Pig III: Spleen. Perl's test. Much hemosiderin is seen.

Fig. 21. Rabbit I: Small intestine. a. Epithelium broken, eroded, and desquamated. b. Mucosa; hemorrhagic area filled with red blood cells; no traces of the glands of Lieberkühn are seen. c. Submucosa. d. Muscularis mucosae, showing hydropic degeneration and numerous vacuoles.

II. CULTIVATION EXPERIMENTS WITH THE BLOOD AND SPINAL FLUID OF PELLAGRINS.

By Edward Francis, Surgeon, U. S. Public Health Service.

Anaërobic cultivation, somewhat after the method described by Noguchi for growing spirochaetae was carried out on the blood of 21 and on the spinal fluid of 16 pellagrins.

METHOD EMPLOYED.

This method of culture involves the use of fresh kidney tissue and ascitic fluid.

KIDNEY TISSUE.

A healthy rabbit is submerged and rubbed until his coat is well soaked in a solution of 5 per cent carbolic acid. While an assistant holds the rabbit vertically, grasping the front feet with one hand and the hind feet with the other, the operator, grasping the rabbit's larynx in his left hand and having a thin-bladed knife in his right hand, thrusts the blade through the soft tissues close to the bodies of the vertebræ and cuts outward, severing all the cervical vessels and surrounding tissues. In an instant the rabbit is dead. He is then quickly nailed to a board and the operator opens the abdominal cavity with an incision from manubrium to symphysis and tacks the abdominal walls to the board. An assistant then raises the lower end of the board until the intestines fall toward the chest, exposing the kidneys. With a sterile hemostatic forceps the operator grasps the kidney at its pelvis and pulls it forward; after the kidney is well raised from its bed it is best to clip the tough ureter with a sterile knife or scissors. The kidney, with forceps attached, is placed in a sterile, covered Petri dish, while the other kidney is similarly removed. With knife or scissors cut away the forceps, which takes away with it the fat of the pelvis. Strip off the capsule. Cut the kidney into 12 pieces. Transfer each piece to a sterile tube, 15 m. m. by 200 m. m., picking up the piece by touching it with a white-hot platinum wire and shaking it loose inside the tube; the tissue will stick to the side of the tube, but it is shaken down to the bottom as you would the mercury in a thermometer. About 2 c. c. of sterile ascitic fluid is then added to each tube and they are allowed to incubate until the next day, when the infected ones are discarded.

ASCITIC FLUID.

My experience with ascitic fluids has not been large enough to justify a discussion of the subject. In this connection color, specific gravity, and bile content are to be considered. Some insist upon an initial specific gravity of at least 1.013 and a freedom from bile; some actually test for neither. Some say the straw-colored fluids are best, yet a greenish or bluish one has proven good. It is said that a fibrinous film in the fluid is essential, and that Berkefeld filtration ruins a fluid.

For my cultures of July 20 I used a straw-colored fluid having a specific gravity of 1.016. On August 5 I used a fluid of a slightly greenish tinge having a specific gravity of 1.020 and on test, an absence of bile. On August 17 I used a straw-colored fluid having a specific gravity of 1.014 and showing an absence of bile when tested.

SOURCE OF MATERIAL.

Blood and spinal fluid were obtained from each of 17 colored pellagrins (cases 1 to 17) at the State Insane Asylum, Milledgeville, Ga., seven of which proved fatal between 6 and 37 days after these materials were obtained. In addition, blood was obtained from 4 mild cases at the Marine Hospital, Savannah, Ga. I am indebted to Dr. W. F. Lorenz for obtaining the spinal fluid for me.

SEEDING.

Blood in 10 c. c. amounts was drawn from the median basilic vein by syringe and was either (*a*) discharged into a flask containing ½ c. c. of a 10 per cent solution of citrate of sodium in saline solution (cases 1 to 11 and cases 19 to 21) or (*b*) discharged into an empty flask in which it was defibrinated with a platinum wire (cases 12 to 18).

SPINAL FLUID.

Spinal fluid obtained by lumbar puncture was allowed to drop from the needle in 10 to 20 c. c. amounts into glass-stoppered bottles.

As soon as collected, each sample of blood or spinal fluid was distributed into a set of eight culture tubes, no two tubes in the set receiving the same amount, but the amounts per tube varied from ½ c. c. to 3 c. c.; in each tube there had been placed, 24 hours previously, a piece of fresh sterile rabbit kidney and 2 c. c of ascitic fluid.

To four of the set of tubes was then added a 4-inch column of ascitic fluid, while to the other four was added a similar column of a mixture of 1 part ascitic fluid and 2 parts of melted and cooled 1 per cent meat-infusion agar, titrated +0.5 to phenolphthalein. The agar used in culturing the blood and spinal fluid of cases 12 to 17 contained in addition 2 per cent glucose. A uniform mixture of the various materials in the tube was obtained by successively drawing them up into a pipette and expelling them again into the tube. Of each set, two tubes of the liquid media and two tubes of the solid media thus inoculated were each covered with a 1-inch column of sterile paraffin oil, while the other four tubes were left uncovered.

All tubes were then incubated without the use of special anaërobic apparatus at 37° C. for two or three weeks, at the end of which time examinations were made with the dark-field microscope.

The method of cultivation employed, furnished conditions of growth suitable for strict anaërobes, strict aërobes, and for facultative organisms of either group. Anaërobic conditions were most nearly approached around the kidney tissue at the bottom of the oil-covered tubes. To a less degree there was anaërobiosis at the bottom of the uncovered tubes. Conditions for aërobic growth were found on the surface of those tubes of media which were not covered with oil.

There were thus studied 8 culture tubes inoculated with 10 c. c. of blood drawn from each of 21 cases, and 8 culture tubes inoculated with 10 to 20 c. c. of spinal fluid drawn from each of 16 cases, making a total of 296 tubes examined.

RESULTS.

The results of the examination of the cultures were negative: the cultures either remained sterile or an occasional tube showed a growth which was evidently a contamination.

APPENDIX.

CASE NOTES.

Case 1.—L. W., colored female. On December 2, 1913, she had sore mouth, diarrhea and eruption on hands and feet.

Blood and spinal fluid cultured July 20, 1914.

Case 2.—R. B., colored female. On May 13, 1914, she had sore mouth, diarrhea, extensive moist eruption on hands and feet, and vaginitis.

Blood and spinal fluid cultured July 20, 1914.

Case 3.—L. G., colored female, admitted July 15, 1914, with sore mouth, diarrhea, moist eruption on hands, forearms, knees, and feet, and with vaginitis.

She died July 26, 1914.

Blood and spinal fluid cultured July 20, 1914.

Case 4.—B. K. S., colored female. On March 1, 1914, she had sore mouth, diarrhea, eruption on hands, feet, and neck.

Blood and spinal fluid cultured July 20, 1914.

Case 5.—K. H., colored female. On May 20, 1914, she had red tongue, diarrhea, and moist eruption on backs of hands and feet.

Blood and spinal fluid cultured July 20, 1914.

Case 6.—K. A., colored female, was admitted April 24, 1914; developed pellagra August 4, 1914, and died of pulmonary tuberculosis October 14, 1914.

Blood and spinal fluid cultured August 5, 1914.

Case 7.—C. H., colored female. On July 24, 1914, she had an eruption on hands, forearms, and feet.

Blood and spinal fluid cultured August 5, 1914.

Case 8.—J. B., colored male, was admitted August 27, 1913, with pellagra. He had a recurrence July 29, 1914, and died of same September 5, 1914.

Blood and spinal fluid cultured August 5, 1914.

Case 9.—J. W., colored male, was admitted with pellagra April 25, 1914, and died of same August 18, 1914.

Blood and spinal fluid cultured August 5, 1914.

Case 10.—K. A. C., colored female. On July 27, 1914, she had sore mouth and eruption on hands and feet.

Blood and spinal fluid cultured August 5, 1914.

Case 11.—J. C., colored male, was admitted July 1, 1914; developed pellagra August 4, 1914, and died of same September 12, 1914.

Blood cultured August 5, 1914.

Case 12.—C. F., colored female. On August 3, 1914, she had a moist eruption on backs of hands and between fingers.

Blood and spinal fluid cultured August 17, 1914.

Case 13.—J. M., colored female, was admitted with pellagra July 17, 1914, and died of same September 2, 1914.

Blood and spinal fluid cultured August 17, 1914.

Case 14.—I. M., colored female, was admitted with pellagra August 11, 1914. The disease was still active September 11, 1914.

Blood and spinal fluid cultured August 17, 1914.

Case 15.—E. D., colored female, was admitted with pellagra June 8, 1914, and died of same September 6, 1914.

Blood and spinal fluid cultured August 17, 1914.

Case 16.—A. O., colored male, was admitted April 8, 1914; developed pellagra August 8, 1914, and died of same September 12, 1914.

Blood and spinal fluid cultured August 17, 1914.

Case 17.—L. B., colored female, was admitted June 10, 1914; developed pellagra August 5, 1914, manifesting an eruption on the backs of the hands.

Blood and spinal fluid cultured August 17, 1914.

Case 18.—G. L. M., white male, age 40, was admitted to the Marine Hospital, Savannah, Ga., September 27, 1914, with red tongue, diarrhea, and an erythema on the backs of hands and fronts of wrists; complained of severe headaches and intense pains in his limbs; said he had attacks of pellagra in 1911 and in spring of 1914. He was discharged November 7, 1914, readmitted February 15, 1915, and again discharged September 11, 1915.

Blood cultured October 7, 1914.

Case 19.—W. H. A., white male, age 59, was admitted to the Marine Hospital October 8, 1914, with diarrhea. His first attack of pellagra was in May, 1914, when the backs of both hands and fronts of both wrists seemed to be sunburned and later peeled off. He was first seen July 29, 1914, at which time he had a very red tongue, but the erythema had nearly disappeared. He was discharged December 12, 1914.

Blood cultured July 29, 1914.

Case 20.—D. L. J., white male, age 40, was admitted to the Marine Hospital July 28, 1914, showing the remains of a dermatitis on the backs of the hands and around the neck. His first attack was in April, 1914. He was discharged 5 days after admission as he was not in need of hospital treatment.

Blood cultured July 29, 1914.

Case 21.—A. H. D., white male, age 65, was admitted to the Marine Hospital July 27, 1914, with an erythema on the backs of the hands and about both elbows. There was no diarrhea. His first attack began about two weeks before admission. He was discharged September 30, 1914.

Blood cultured July 27, 1914.

III. FURTHER ATTEMPTS TO TRANSMIT PELLAGRA TO MONKEYS.

By **Edward Francis**, Surgeon, United States Public Health Service.

Systematic attempts on the part of the United States Public Health Service to infect monkeys with pellagra were begun in 1912 under the direction of Surg. C. H. Lavinder while in charge of pellagra investigations at the United States Marine Hospital, Savannah, Ga., assisted by Passed Asst. Surg. R. M. Grimm.

On account of the report by Harris,[1] of New Orleans, of the successful transmission of pellagra to a rhesus monkey, the scope of the work at Savannah was very much extended in July, 1913, and it was at that time that the writer became identified with the investigations. A short time later Dr. W. F. Lorenz, director of the Wisconsin Psychopathic Institute, Mendota, Wis., was engaged by the Public Health Service as a special expert for the study of the mental manifestations of the disease. While prosecuting his special studies at the State insane asylum, Milledgeville, Ga., he cooperated in some of the work here reported.

The studies of the above-named officers were reported[2] in September, 1914. Prior to this time, however, Drs. Lavinder and Grimm (in April) and Dr. Lorenz (by September 1) had discontinued their connection with the work.

In the above report, 74 rhesus monkeys and 3 baboons, after having been subjected to multiple inoculations in various ways with various kinds of pellagrous material from many pellagrins, were reported as healthy and showing no evidence that was considered as a pellagrous infection.

In the present paper the details of the animal inoculations begun by Drs. Lavinder and Grimm and continued and extended by the writer are submitted.

Details are presented as to the character of the pellagrous lesions manifested at autopsies from which inoculation material was obtained, the time intervals between death and autopsy and between autopsy and injection of animals, the kinds and amounts of pellagrous materials used, and the method of injection and number of monkeys employed.

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[1] Harris: The Experimental Production of Pellagra in the Monkey, etc., The Journal A. M. A., June 21, 1913, p. 1948.

[2] Lavinder, Francis, Grimm, and Lorenz: Attempts to Transmit Pellagra to Monkeys (Journal A. M. A., 1914, September 26, Vol. LXIII, p. 1093).

INJECTION OF NERVOUS TISSUE.

The brain, spinal cord, and their membranes were removed at eight autopsies, ground in a meat grinder, mixed with an equal volume of normal saline solution, and allowed to extract in the ice box for varying periods. The suspension was then squeezed through six thicknesses of gauze. The gauze filtrate was either injected into animals without further treatment or injected after filtration through a Berkefeld filter.

Gauze filtrate.—At autopsy No. 1, performed 3 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and was injected on July 30, 1913, 27 hours after death, intracerebrally (1 c. c.), intravenously (3 c. c.), and subcutaneously (4 c. c.) into rhesus No. 51, which died a year later, July 12, 1914, of tuberculosis. Rhesus No. 52 was injected with the same kind of material in the same amounts, in the same locations, and at the same time as was rhesus No. 51; this animal died 6 weeks later (Aug. 31, 1913) from cerebral abscess.

At autopsy No. 2, performed 1 hour after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected August 18, 1913, 22 hours after death, intracerebrally (1 c. c.) and intravenously (5 c. c.) into rhesus No. 57, which died 2 months later (Oct. 26, 1913) from cerebral abscess.

At autopsy No. 3, performed 12 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected in one-half c. c. amounts daily intravenously into rhesus No. 19 for 4 consecutive days, the first injection being made 38 hours after death of the patient from which the autopsy material was obtained.

At autopsy No. 4, performed 8 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected October 29, 1913, 33 hours after death, intraspinally (1 c. c.) into rhesus No. 41. The same kind of material was injected 57 hours after death intravenously (2 c. c.) into rhesus No. 49.

At autopsy No. 8, performed 8 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected April 13, 1914, 58 hours after death, intraspinally in 4 c. c. amounts into rhesus monkeys Nos. 1, 2, 3, 5, 6, 25, 38, 45, 49, 61, and 62. Monkey No. 2 died 14 months later (June 24, 1915) from acute effects of injection of material of another kind; Nos. 25 and 38 died 10 months later (Feb. 18, 1915) of tuberculosis.

At autopsy No. 9, performed 5 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected May 27, 1914, 11 hours after death, into six monkeys. Rhesus monkeys Nos. 114, 115, 116, and 121 each received 2 c. c. intraspinally and 2 c. c. intraperitoneally; rhesus No. 119 received 1 c. c. intracerebrally and 1 c. c. intramuscularly; rhesus No. 120 received 1 c. c. intracerebrally and 1 c. c. intraperitoneally; monkey No. 114 died, 14 months after the inoculation, of tuberculosis; Nos. 119 and 120 died 13 months later from the acute effects of another inoculation.

At autopsy No. 10, performed 9 hours after death, a gauze filtrate was prepared from the brain, spinal cord, and their membranes and injected June 3, 1914, 14 hours after death, intracerebrally (1 c. c.) and intraperitoneally (1 c. c.) into rhesus monkey No. 123; intracerebrally (1 c. c.) and intramuscularly (1 c. c.) into rhesus No. 117.

Berkefeld filtrate.—At autopsy No. 8, performed 8 hours after death, a Berkefeld filtrate of the brain, spinal cord, and their membranes was prepared and injected April 13, 1914, 16 hours after death, intraspinally in 4 c. c. amounts into rhesus monkeys Nos. 26, 38, and 39. No. 38 died 10 months later (Feb. 19, 1915) of tuberculosis; No. 39 died 15 months later (July 31, 1915) from cause not apparent at autopsy.

At autopsy No. 6, performed 13½ hours after death, a Berkefeld filtrate was prepared from the brain, spinal cord, and their membranes and injected January 21 and January 22, 1914, 36 and 60 hours after death, intraspinally in 5 c. c. amounts at each time into rhesus No. 84. This animal died 15 months later (May 1, 1915) from tuberculosis.

The details of each of these experiments using brain, spinal cord, and their membranes are shown in the following table:

TABLE NO. 1.—*Injection of brain, spinal cord, and their membranes.*

(A) GAUZE FILTRATE.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1913.							
July 30	No. 1...	3	24	Cerebrum..... Vein.......... Subcutaneous.	1 3 4	Rhesus 51...	No. 51 died July, 1914. Tuberculosis.
Do..	No. 1...	3	24	Cerebrum..... Vein.......... Subcutaneous.	1 3 4	Rhesus 52...	No. 52 died August, 1913. Brain abscess.
Aug 18	No. 2...	1	21	Cerebrum..... Vein..........	1 5	Rhesus 57...	No. 57 died October, 1913. Brain abscess.
Oct. 13-16.	No. 3...	12	26 to 84	Vein	½ (daily)	Rhesus 19...	
Oct. 29	No. 4...	8	25	Spine.........	1	Rhesus 41...	
Oct. 30	No. 4...	8	49	Vein..........	2	Rhesus 49...	

Table No. 1.—*Injection of brain, spinal cord, and their membranes*—Continued.

(A) GAUSE FILTRATE—Continued.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. C. inoculation.	Monkey No.	Remarks.
1914.							
Apr. 13	No. 8...	8	50	Spine.........	4	Rhesus 1, 2, 3, 5, 6, 25, 38, 45, 49, 61, and 62.	No. 2 died June, 1915, due to an injection. No. 25 died February, 1915. Tuberculosis. No. 38 died February, 1915. Tuberculosis.
May 27	No. 9...	5	6	Spine......... Peritoneum...	2 2	Rhesus 114, 115, 116, and 121.	No. 114 died July, 1915. Tuberculosis.
Do..	No. 9...	5	6	Cerebrum..... Muscle........	1 1	Rhesus 119..	No. 119 died June, 1915, due to an injection.
Do..	No. 9...	5	6	Cerebrum..... Peritoneum...	1 1	Rhesus 120..	No. 120 died June, 1915, due to an injection.
June 3	No. 10..	9	5	Cerebrum..... Peritoneum...	1 1	Rhesus 123..	
Do..	No. 10..	9	5	Cerebrum..... Muscle........	1 1	Rhesus 117..	

(B) BERKEFELD FILTRATE.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. C. inoculation.	Monkey No.	Remarks.
Jan. 21	No. 6...	13½	22½	Spine.........	5	Rhesus 84...	No. 84 died May, 1915. Tuberculosis.
Jan. 22	No. 6...	13½	46½	.....do........	5		
Apr. 13	No. 8...	8	8	.....do........	4	Rhesus 26, 38, and 39.	No. 38 died February, 1915. Tuberculosis. No. 39 died July, 1915, from cause not apparent at autopsy.

INJECTION OF BUCCAL, THORACIC, AND ABDOMINAL ORGANS EXCEPT INTESTINES.

At autopsy No. 8, performed eight hours after death, the buccal, thoracic, and abdominal contents, including tongue, salivary glands, tonsils, oesophagus, lungs, heart, diaphragm, stomach, liver, spleen, kidneys, omentum, and mesentery, but not including the intestines, were removed and all ground in a meat grinder. A portion of this material was treated with saline solution and allowed to stand in the ice box four hours, after which it was squeezed through gauze.

Gauze filtrate.—A portion of the gauze filtrate was injected (*a*) April 11, 1914, 16 hours after death, intravenously (1 c. c.) and subcutaneously (1 c. c.) into rhesus monkeys Nos. 41, 45, 47, and 49; (*b*) April 13, 1914, 60 hours after death, intravenously (9 c. c.) and subcutaneously (1 c. c.) into rhesus monkeys Nos. 32, 33, and 34. No. 32 died June 22, 1915, and No. 33 died March 7, 1915, both from tuberculosis. (See Table No. 2.)

Berkefeld filtrate.—Another portion of the gauze filtrate was passed through a Berkefeld filter and was injected April 11, 1914, 16 hours after death, intravenously (10 c. c.) into rhesus monkeys Nos. 27, 28, and 58. No. 58 died July 8, 1915, from the acute effects of an injection of another character.

These experiments are set forth in tabular form as follows:

TABLE No. 2.—*Injection of buccal, thoracic, and abdominal organs, except intestines.*

(A) GAUZE FILTRATE.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1914.							
Apr. 11	No. 8...	8	8	Vein.......... Subcutaneous.	1 1	Rhesus 41, 45, 47, and 49.	
Apr. 13	No. 8...	8	52	Vein.......... Subcutaneous.	9 1	Rhesus 34...	
Do....	No. 8...	8	52	Vein.......... Subcutaneous.	9 1	Rhesus 32...	No. 32 died June, 1915. Tuberculosis.
Do....	No. 8...	8	52	Vein.......... Subcutaneous.	9 1	Rhesus 33...	No. 33 died Mar., 1915. Tuberculosis.

(B) BERKEFELD FILTRATE.

1914. Apr. 11	No. 8...	8	8	Vein..........	10	Rhesus 27, 28, and 53.	No. 58 died July, 1915, due to an injection.

INJECTION OF INTESTINES AND CONTENTS.

The intestines and fecal contents were removed at autopsies Nos. 1, 2, 3, 4, 6, 7, and 8, ground in a meat grinder, extracted with saline solution for approximately 10, 4, 12, 12, 12, 3, and 12 hours, respectively, and then squeezed through gauze. The gauze filtrates were either injected into animals without further treatment or injected after Berkefeld filtration.

Gauze filtrate.—A portion of the gauze filtrate from autopsy No. 2, performed 1 hour after death, was injected August 18, 1913, 22 hours after death, intravenously (2 c. c.) into java monkey No. 63, which died October 5, 1913, from cause not apparent at autopsy.

A portion of the gauze filtrate from autopsy No. 3, performed 12 hours after death, was injected October 13, 1913, 38 hours after death, intravenously (1 c. c.) into rhesus No. 21. This animal died March 16, 1914, from tuberculosis.

A portion of the gauze filtrate from autopsy No. 4, performed 8 hours after death, was injected (*a*) October 29, 1913, 36 hours after death, intravenously (2 c. c.) into rhesus monkeys 45 and 47. (*b*) November 4 and 8, 7 and 11 days, respectively, after death, intravenously (1 c. c. each time) into rhesus No. 25. This animal died February 18, 1915, from tuberculosis.

A portion of the gauze filtrate from autopsy No. 6, performed 13½ hours after death, was injected (*a*) January 21, 1914, 36 hours after death, intravenously (2 c. c.) into rhesus monkeys 85 and 86. (*b*) January 22, 1914, 60 hours after death, intravenously (2 c. c.) into rhesus monkeys Nos. 85 and 86.

A portion of the gauze filtrate from autopsy No. 7, performed 3 hours after death, was injected February 4, 1914, 8 hours after death, intravenously (1 c. c.) into rhesus No. 91.

Berkefeld filtrate.—A portion of the gauze filtrate from autopsy No. 1, performed 3 hours after death, was passed through a Berkefeld filter and injected July 30, 1913, 27 hours after death, intracerebrally (1 c. c.), intravenously (12 c. c.), and subcutaneously (3 c. c.) into rhesus No. 53.

A portion of the gauze filtrate from autopsy No. 2, performed 1 hour after death, was passed through a Berkefeld filter and injected August 18, 1913, 22 hours after death, intracerebrally (1 c. c.) and intravenously (7 c. c.) into baboon No. 64.

A portion of the gauze filtrate from autopsy No. 8, performed 8 hours after death, was passed through a Berkefeld filter and injected (*a*) April 12, 1914, 36 hours after death, intravenously (9 c. c.) and subcutaneously (1 c. c.) into each of rhesus monkeys Nos. 1, 2, 3, 5, 6, and 62. No. 2 died June 24, 1915, from the acute effects of an injection of other material. (*b*) April 13, 1914, 60 hours after death, intravenously (9 c. c.) and subcutaneously (1 c. c.) into rhesus monkeys Nos. 36, 37, 39, and 40. No. 39 died July 31, 1915, from cause not apparent at autopsy. (*c*) April 18, 1914, 1 week after death, intravenously (9 c. c.) and subcutaneously (1 c. c.) into rhesus monkeys Nos. 1, 2, 3, and 5. As above recorded, No. 2 died from the acute effects of an injection of other material.

Feces collected at autopsy No. 2 on August 17 were passed through a Berkefeld filter on August 18, and 15 c. c. of the filtrate were injected between August 18 and September 17, 1913, intravenously into female baboon No. 66, in amounts not to exceed 1 c. c. in any one day.

These experiments are set forth in tabular form as follows:

TABLE No. 3.—*Injection of intestines and contents.*

(A) GAUZE FILTRATE.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1913. Aug. 18	No. 2...	1	21	Vein..........	2	Java 63.....	No. 63 died Oct. 5, 1913, from cause not apparent at autopsy.
Oct. 13	No. 3...	12	26	.....do........	1	Rhesus 21...	No. 21 died Mar. 16, 1914, tuberculosis.
Oct. 29	No. 4...	8	28	.....do........	2	Rhesus 45 and 47.	
Nov. 4	No. 4...	8	160	.....do........	1	Rhesus 25...	No. 25 died Feb. 16, 1915; tuberculosis.
Nov. 8	No. 4...	8	256	.....do	1	Rhesus 25...	
1914. Jan. 21	No. 6...	13½	22½	.....do........	2	Rhesus 85 and 86.	
Jan. 22	No. 6...	13½	46½	.....do........	2	.....do......	
Feb. 4	No. 7...	3	5	.....do........	1	Rhesus 91...	

TABLE No. 3.—*Injection of intestines and contents*—Continued.

(B) BERKEFELD FILTRATE.

Date of inoculation.	Source of material, autopsy.	Hours between death and autopsy.	Hours between autopsy and inoculation of animals.	Site of injection.	C. C. inoculated.	Monkey No.	Remarks.
1913.							
July 30	No. 1...	3	24	Cerebrum Vein	1 12	Rhesus 53...	
Aug. 18	No. 2...	1	21	Subcutaneous Cerebrum Vein	3 1 7	Baboon 64..	
Aug. 18 to Sept. 17	No. 2...	1	....	Vein	15	Baboon 66..	
1914.							
Apr. 12	No. 8...	8	28	Vein Subcutaneous	9 1	Rhesus 1, 2, 3, 5, 6, and 62.	No. 2 died June 24, 1915, due to an injection.
Apr. 13	No. 8...	8	52	Vein Subcutaneous	9 1	Rhesus 36, 37, 39, and 40.	No. 39 died July 31, 1915, from cause not apparent at autopsy.
Apr. 18	No. 8...	8	160	Vein Subcutaneous	9 1	Rhesus 1, 2, 3, and 5.	No. 2 died June 24, 1915, due to an injection.

INJECTION OF SKIN.

Skin, showing the pellagrous lesions, obtained from five autopsies, was ground in a meat grinder, treated with saline solution, and squeezed through gauze. A portion was used for inoculation without further treatment; another portion was first passed through a Berkefeld filter.

Gauze filtrate.—A portion of the gauze filtrate from autopsy No. 1, performed 3 hours after death, was injected July 30, 1913, 27 hours after death, intracerebrally (1 c. c.), intravenously (5 c. c.), and subcutaneously (3 c. c.) into rhesus No. 54, which died February 11, 1914, from tuberculosis.

A portion of the gauze filtrate from autopsy No. 2, performed 1 hour after death, was injected August 18, 1913, 22 hours after death, intracerebrally (1 c. c.) and intravenously (4 c. c.) into Java monkey No. 59, which died October 9, 1913, from oesophagastomum infection.

A portion of the gauze filtrate from autopsy No. 3, performed 12 hours after death, was injected (*a*) October 13, 1913, 38 hours after death, intravenously (1 c. c.) into rhesus No. 17, which died October 26, 1915, from cause not apparent at autopsy; (*b*) October 13 to 17 intravenously (1 c. c. daily) into rhesus No. 18.

A portion of the gauze filtrate from autopsy No. 4, performed 8 hours after death, was injected October 29, 1913, 36 hours after death, intravenously (2 c. c.) and subcutaneously (1 c. c.) into rhesus monkeys Nos. 38, 39, and 40. No. 38 died February 19, 1915, from tuberculosis. No. 39 died July 31, 1915, from cause not apparent at autopsy.

A portion of the gauze filtrate from autopsy No. 6, performed 13½ hours after death, was injected January 21, 1914, 36 hours after death, intravenously (2 c. c.) into rhesus No. 87.

Berkefeld filtrate.—A portion of the gauze filtrate from autopsy No. 2, performed 1 hour after death, was filtered through a Berkefeld filter and injected August 18, 1913, 22 hours after death, intracerebrally (1 c. c.), intravenously (9 c. c.), and subcutaneously (5 c. c.) into rhesus monkeys Nos. 61 and 62.

These experiments are set forth in tabular form as follows:

TABLE No. 4.—*Injection of skin.*

(A) GAUZE FILTRATE.

Date of inoculation.	Source of material, autopsy	Hours between death and collection of autopsy material.	Hours between collection of material and inoculation of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1913. July 30	No. 1	3	24	Cerebrum Vein Subcutaneous.	1 5 3	Rhesus 54	No. 54 died Feb., 1914; tuberculosis.
Aug. 18	No. 2	1	21	Cerebrum Vein	1 4	Java 59	No. 59 died Oct. 9, 1913; oesophagostomum.
Oct. 13	No. 3	12	26	Vein	1	Rhesus 17	No. 17 died Oct. 26, 1915, from cause not apparent at autopsy.
Oct. 13-17	No. 3	12	....	Vein	1 (daily)	Rhesus 18	
Oct. 29	No. 4	8	28	Vein Subcutaneous.	2 1	Rhesus 38, 39 and 40	No. 38 died Feb., 1915, tuberculosis. No. 39 died July, 1915, from cause not apparent at autopsy.
1914. Jan. 21	No. 6	13½	22½	Vein	2	Rhesus 87	
(B) BERKEFELD FILTRATE.							
1913. Aug. 18	No. 2	1	21	Cerebrum Vein Subcutaneous.	1 9 5	Rhesus 61 and 62.	

INJECTION OF BLOOD.

Blood was drawn from the median basilic veins of eight pellagrins (cases 1 to 8) and after being either defibrinated or citrated was immediately injected.

The condition of the pellagrins from whom the blood was obtained may be stated briefly as follows:

Cases 1, 3, and 4 were severe but nonfatal white males, showing marked eruptions and diarrhea at the time of bleeding.

Case 2 at the time of bleeding showed no eruption but was very much disordered mentally.

Cases 5, 6, 7, and 8 were colored females, showing marked skin lesions and diarrhea at the time of bleeding. They died 10, 33, 13, and 7 days, respectively, after the date on which their blood was drawn.

Defibrinated blood.—Blood was drawn from case 1 on August 26, 1913, and after defibrination was injected intravenously (8 c. c.) into rhesus No. 68. Blood was drawn from case 2 September 29, 1913, and after defibrination was injected intravenously (8½ c. c.) into the same monkey. No. 68 died January 8, 1914, from tuberculosis.

Blood was drawn from case 3 June 6, 1914, and after defibrination was injected intraspinally (5 c. c.) and intramuscularly (10 c. c.) into each of two rhesus monkeys, Nos. 85 and 86.

Citrated blood.—Thirty-five c. c. of blood were drawn from case 4 on June 6, 1914, and mixed with 0.3 c. c. of a 10 per cent solution of citrate of sodium, after which 10 c. c. were injected intramuscularly into each of three rhesus monkeys, Nos. 10, 72, and 76. No. 10 died June 19, 1915, from the acute effects of an injection of other material. No. 76 died July 26, 1915, from tuberculosis.

Mixed blood.—Twenty c. c. of blood were drawn from cases 5, 7, and 8 each on May 20, 1914, each into 0.2 c. c. of 10 per cent citrate of sodium. The same amount at the same time was drawn from case 6 and was defibrinated. The four bloods were then mixed and the mixture was injected intravenously (6 c. c.) and intraperitoneally (6 c. c.) into each of rhesus monkeys Nos. 72, 76, 85, and 86, and intraperitoneally (10 c. c.) into No. 10. No. 10 died June 19, 1915, from the acute effects of an injection of other material.

These experiments are set forth in tabular form as follows:

TABLE No. 5.—*Injection of blood.*

(A) DEFIBRINATED.

Date of injection.	Pellagrins who furnished the blood.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1913.					
Aug. 26	Case 1...	Vein........	8	Rhesus 68.....	No. 68 died Jan. 8, 1914. Tuberculosis.
Sept. 29	Case 2...	.....do......	8½	.....do........	
1914.					
June 6	Case 3..	Spine....... Muscle......	5 10	Rhesus 85 and 86.	
(B) CITRATED.					
June 6	Case 4...	Muscle......	10	Rhesus 10, 72, and 76.	No. 10 died June, 1915, due to an injection. No. 76 died July, 1915. Tuberculosis.
(C) DEFIBRINATED OR CITRATED, MIXED.					
May 20	Case 5...	Vein....... Peritoneum.	6 6	Rhesus 72, 76, 85, and 86.	No. 76 died July, 1915. Tuberculosis.
	Case 6... Case 7... Case 8...	Peritoneum.	10	Rhesus 10.....	No. 10 died June, 1915, due to an injection.

INJECTION OF CEREBROSPINAL FLUID COLLECTED AT AUTOPSY.

Not filtered.—Spinal fluid collected at autopsy No. 2, performed 1 hour after death, was injected August 18, 1913, 22 hours after death, without filtration, intracerebrally (1 c. c.) and intravenously (5 c. c.) into rhesus No. 58, which died July 8, 1915, from the acute effects of an injection of another character.

Spinal fluid collected at autopsy No. 4, performed 8 hours after death, was injected August 28, 1913, 15 hours after death, without filtration, intraspinally (1 c. c.) into rhesus No. 26, intraspinally (2 c. c.) into rhesus No. 27, intraspinally (3 c. c.) into rhesus No. 28, intraspinally (4½ c. c.) into rhesus No. 58.

Spinal fluid collected at autopsy No. 6, performed 13½ hours after death, was injected January 20, 1914, 12 hours after death, without filtration, intraspinally (5 c. c.) into rheus No. 80.

Berkefeld filtrate.—Spinal fluid collected at autopsy No. 7, performed 3 hours after death, was injected February 4, 1914, 8 hours after death, after filtration through a Berkefeld filter, intraspinally (5 c. c.) into rhesus monkeys Nos. 26, 27, 28, and 58.

Spinal fluid collected at autopsy No. 8, performed 8 hours after death, was injected April 11, 1914, 12 hours after death, after filtration through a Berkefeld filter, intraspinally (5 c. c.) into rhesus monkeys Nos. 32, 33, 34, 35, 36, and 37. Nos. 32 and 33 died June 22, 1915, and March 7, 1915, respectively, from tuberculosis.

These experiments are set forth in tabular form as follows:

TABLE No. 6.—*Injection of cerebrospinal fluid collected at autopsy.*

(A) NOT FILTERED.

Date of injection.	Source of material. Autopsy.	Hours between death and collection of autopsy material.	Hours between collection of material and injection of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
1913.							
Aug. 18	No. 2...	1	21	Cerebrum.....	5	58	No. 58 died July, 1915, due to an injection.
				Vein..........	5	58	
Oct. 28	No. 4...	8	7	Spine.........	1	26	
Do....	No. 4...	8	7	.....do........	2	27	
Do....	No. 4...	8	7	.....do........	3	28	
Do....	No. 4...	8	7	.....do........	4½	58	No. 58 died (see above).
1914.							
Jan. 20	No. 6...	13½	3½	.....do........	5	80	

(B) BERKEFELD FILTRATE.

Date of injection.	Source of material. Autopsy.	Hours between death and collection of autopsy material.	Hours between collection of material and injection of animals.	Site of injection.	C. c. inoculated.	Monkey No.	Remarks.
Feb. 4	No. 7...	3	5	Spine.........	5	Rhesus 26, 27, 28, and 58.	No. 58 died July, 1915, due to an injection.
Apr. 11	No. 8...	8	4	.....do........	5	Rhesus 32, 33, 34, 35, 36, and 37.	No. 32 died June, 1915. Tuberculosis. No. 33 died March, 1915. Tuberculosis.

INJECTION OF SPINAL FLUID COLLECTED DURING LIFE.

Spinal fluid collected during life from 28 pellagrins (cases 29 to 54 and cases 3 and 4) was injected without filtration immediately after collection, in amounts of 5 c. c. or more intraspinally into 24 rhesus monkeys, 1 receiving 5 injections of approximately 5 c. c. each, another receiving 4 such injections, another receiving 3 injections, 16 others receiving 2 injections, and 5 others receiving only 1 injection each.

Brief data as to symptoms manifested by pellagrins from whom spinal fluid was drawn will be found by reference to case numbers in the case notes.

Twenty-three of the pellagrins who furnished spinal fluid (cases 29 to 51) were colored females at the State insane asylum, Milledgeville, Ga. Pellagrins 52, 53, 54, 3, and 4 were white males at the Marine Hospital, Savannah, Ga.

Dr. W. F. Lorenz drew the fluid from all these patients and injected the monkeys while conducting for the Public Health Service his studies upon the mental manifestations of the disease.

Of the 24 monkeys inoculated, all are still well[1] except 6; 5 of the 6 lived over a year following their last injection and died from causes plainly other than the spinal injections, while the sixth died from tuberculosis six and one-half months after his last injection.

These experiments are set forth in tabular form as follows:

TABLE NO. 7.—*Injection of spinal fluid drawn during life.*

Date of injection.	Case No. of pellagrin who furnished spinal fluid.	Site of injection.	C. C. injected.	Rhesus monkey No.	Remarks.
1914.					
Apr. 14	29	Spine	5	98	
May 2	30	...do	4	98	
Apr. 14	31	...do	6	99	
May 2	32	...do	5	99	
May 7	33	...do	4	99	
May 19	34	...do	7	99	
May 30	35	...do	5	99	
Apr. 20	36	...do	6	100	No. 100 died December, 1914; tuberculosis.
May 2	37	...do	4	100	
May 19	38	...do	6	100	
May 30	39	...do	5	100	
Apr. 17	40	...do	8	101	No. 101 died June, 1915, due to an injection.
May 19	38	...do	5	101	
May 30	35	...do	5	101	
May 19	41	...do	5	107	
May 30	39	...do	5	107	
May 19	41	...do	5	108	
May 30	42	...do	5	108	
May 19	34	...do	6	109	
May 30	42	...do	5	109	
June 12	43	...do	9	102	
July 10	44	...do	5	102	
June 12	45	...do	8	103	

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[1] At time this report was written, December, 1915.

TABLE No. 7.—*Injection of spinal fluid drawn during life*—Continued.

Date of injection.	Case No. of pellagrin who furnished spinal fluid.	Site of injection.	C. C. injected.	Rhesus monkey No.	Remarks.
1914.					
July 10	46	Spine....	5	103............	
June 12	47	...do.....	8	104............	
July 10	44	...do.....	5	104............	
June 12	48	...do.....	6	105............	No. 105 died October, 1915, from cause not apparent at autopsy.
July 10	42	...do.....	5	105............	
June 12	49	...do.....	7	106............	
July 10	50	...do.....	5	106............	
June 12	51	...do.....	8	110............	
July 10	46	...do.....	5	110............	
May 13	52	...do.....	5	19, 28, and 58..	No. 58 died July, 1915, due to an injection.
May 13	53	...do.....	5	26, 27, 80, and 84.	No. 84 died May, 1915; tuberculosis.
May 13	54	...do.....	5	71, 73, 81, and 82.	No. 82 died July, 1915, due to an injection.
June 2	3	...do.....	9	71, 81, and 82..	No. 82 died. (See above.)
June 2	4	...do.....	9	26, 27, and 80..	

INJECTION OF PERICARDIAL FLUID.

Pericardial fluid collected at autopsy No. 6, performed 13½ hours after death, was injected without filtration January 20, 1914, 17 hours after death, intravenously (10 c. c.), and injected in 10 c. c. amounts intravenously daily thereafter for four days into two rhesus monkeys, Nos. 81 and 82. No. 82 died July 2, 1915, from the acute effects of an injection of other material.

A portion of the pericardial fluid collected at autopsy No. 6 was passed through a Berkefeld filter and injected January 23 and January 26, three and six days, respectively, after death, intraspinally in 5 c. c. amounts each time into rhesus monkeys Nos. 71 and 73.

INJECTION OF URINE.

Urine from four pellagrins, cases 9, 10, 11, and 12, each of whom showed a marked indican reaction, was injected intravenously after Berkefeld filtration into five rhesus monkeys. All urine injected had been passed within 24 hours.

Case 9 was acute, showing skin eruption. Case 10 was in his fourth yearly attack, presenting eruption on both forearms. Case 11 was in his third attack and manifested an eruption on elbows and hands. Case 12 was a severe fatal case, with sore mouth, diarrhea, and marked wet lesions on both hands and wrists.

The mixed urine of cases 9, 10, and 11 was injected between November 26 and December 8, 1913, in daily amounts of either 10 c. c. or 20 c. c. intravenously into rhesus monkeys Nos. 10, 72, and 76, and in total amounts, respectively, of 130 c. c., 155 c. c., and 155 c. c.

The mixed urine of cases 9 and 12 was injected between April 8 and 13, 1914, in daily amounts of either 10 c. c. or 20 c. c., intravenously, into rhesus monkeys Nos. 10, 76, 93, and 94, each receiving, respectively, 85 c. c., 115 c. c., 90 c. c., and 105 c. c. Rhesus No. 10 died June, 1915, from an injection of other material; No. 76 died July, 1915, from tuberculosis; No. 93 died March, 1915, from monkey birth.

These experiments are set forth in tabular form as follows:

TABLE NO. 8.—*Injcction of Berkefeld filtrate of urine.*

Date of injection.	Pellagrins who furnished the urine.	Site of injection.	Total c. c. injected.	Monkey No.	Remarks.
1913. Nov. 26 to Dec. 8.	Cases 9, 10, and 11 mixed..	Vein....	130	Rhesus 10...	No. 10 died June, 1915, due to an injection of other material.
		..do....	155	Rhesus 76...	No. 76 died July, 1915; tuberculosis.
		..do....	155	Rhesus 72...	
1914. Apr. 8-13...	Cases 9 and 12 mixed.....	..do....	105	Rhesus 94...	
		..do....	85	Rhesus 10...	No. 10 died. (See above.)
		..do....	115	Rhesus 76...	No. 76 died. (See above.)
		..do....	90	Rhesus 93...	No. 93 died March, 1915, from monkey birth.

INJECTION OF FECES.

Feces from pellagrins (cases 13, 14, and 15), after Berkefeld filtration, were injected intraperitoneally into 26 rhesus monkeys. All three cases at the time of stool filtration were passing through acute severe nonfatal attacks, accompanied by erythema and diarrhea.

Diarrheal stools, free from urine, collected morning and evening from cases 13, 14, and 15 were subjected daily to filtration through paper with the use of a Buchner filter and a vacuum, but without the use of a diluent. The paper filtrates were passed through Berkefeld filters, letter N, without the use of a diluent and the mixed sterile filtrates were injected daily between June 17 and 23, 1915, intraperitoneally, using 10 c. c. for the first injection and 20 c. c. for subsequent injections into each of 26 rhesus monkeys. Ten of this number died from acute peritonitis within a week from their last injection. Three others died from tuberculosis 30, 42, and 104 days, respectively, after their last injection. Two died from causes not apparent at autopsy. The remaining 11, aside from some depression following the injections, have remained well. The numbers of the 11, and total amount of undiluted fecal filtrate received by each of them, are as follows:

No. 1, 90 c. c.; No. 3, 110 c. c.; No. 13, 110 c. c.; No. 19, 40 c. c.; No. 37, 60 c. c.; No. 78, 40 c. c.; No. 91, 60 c. c.; No. 98, 100 c. c.; No. 99, 130 c. c.; No. 108, 60 c. c.; No. 109, 60 c. c.

These experiments are set forth in tabular form as follows:

TABLE NO. 9.—*Injection of Berkefeld filtrate of feces.*

Date of injection.	Source of material.	Site of injection.	Total c. c. injected.	Monkey No.	Remarks.
1915. June 17-23	Feces of pellagrins, cases 13, 14, and 15, mixed.	Peritoneum...	90	1	Still well Nov. 26, 1915.
			110	3	Do.
			110	13	Do.
			40	19	Do.
			60	37	Do.
			40	78	Do.
			60	91	Do.
			100	98	Do.
			130	99	Do.
			60	108	Do.
			60	109	Do.
			120	17	Died Oct. 26, 1915, from cause not apparent at autopsy.
			130	97	Died Oct. 5, 1915; tuberculosis.
			130	111	Died Sept. 18, 1915, from cause not apparent at autopsy.
			60	77	Died Aug. 4, 1915; tuberculosis.
			80	24	Died July 21, 1915; tuberculosis.
			60	2	2, 9, 10, 11, 14, 58, 82, 101, 119, and 120 all died from peritonitis within a week from their last injection.
			90	9	
			30	10	
			50	11	
			90	14	
			90	58	
			90	82	
			110	101	
			70	119	
			110	120	

INTRANASAL APPLICATION OF UNTREATED FECES.

Feces from cases 16, 17, and 18 were engaged on cotton pledgets in the nasal fossæ of 29 rhesus monkeys. Case 16 was a fatal case with diarrhea, presenting at autopsy loosened epidermis on backs of both hands and fronts of both wrists, roughened skin over the ridge of nose, red tongue, foul mouth, and liquid feces.

Case 17 was a nonfatal case in his first attack, with erythema on both hands and elbows; no diarrhea.

Case 18 was in his first attack, manifesting erythema of hands, sore mouth, and diarrhea.

On September 12, 1914, at the autopsy of case 16, the small and large intestines from the pyloric end of the stomach to the anus, including the liquid contents, were removed in one piece and placed in the ice box until September 17, on which date the entire intestinal tract was laid open with a scissors and the mucous membrane was scraped throughout with a dull edge. The liquid fecal contents and the scrapings were removed and placed in the ice box until September 18, when two-thirds of the case 16 material was mixed with a fresh stool from case 17. This fecal mixture was applied on September 18 to the nasal fossæ of rhesus monkeys Nos. 8, 9, 14, 38, 76, 81, 82, 98, 99, 100, 101, 104, 105, 106, 107, 115, 116, 117, 119, 120, and 123.

On September 19 the remaining one-third of the case 16 material was mixed with a fresh stool from case 18 and applied to the nasal fossæ of monkeys Nos. 28, 72, 103, 108, 109, 110, 114, and 121.

Of the 31 monkeys which received intranasal application of feces, 17 have remained well; the other 12, Nos. 8, 9, 14, 38, 76, 82, 100, 101, 105, 114, 119, and 120, died from causes evidently other than the intranasal applications.

The infectivity of feces on the conjunctiva was also tested.

FEEDING OF SPUTUM.

Sputum collected fresh each day from 10 spitting pellagrins was fed by stomach tube to 5 rhesus monkeys, Nos. 9, 14, 16, 23, and 77, each receiving between 25 c. c. and 100 c. c. at a feeding, and receiving a total of 3,630 c. c., 1,650 c. c., 2,220 c. c., 1,580 c. c., and 915 c. c., respectively.

Rhesus No. 9 was fed in November, 1913, with 700 c. c. sputum from case 19; in February, 1914, with 1,030 c. c. from cases 23 and 24; in March, 1914, with 1,900 c. c. from cases 23, 24, and 12; total, 3,630 c. c. Rhesus No. 9 died June 28, 1915, from the acute effects of an injection of other material.

Rhesus No. 14 was fed in November, 1913, with 300 c. c. sputum from case 22 and 350 c. c. from case 21; in March, 1914, with 1,000 c. c. from case 12; total, 1,650 c. c. Rhesus No. 14 died June 23, 1915, from the acute effects of an injection of other material.

Rhesus No. 16 was fed in November, 1913, with 980 c. c. from case 25; in December, 1913, with 200 c. c. from case 25; in March, 1914, with 1,040 c. c. from case 12; total, 2,220 c. c.

Rhesus No. 23 was fed in November, 1913, with 365 c. c. from case 20 and 300 c. c. from case 26; in December, 1913, with 115 c. c. from case 20; in March, 1914, with 800 c. c. from case 12; total, 1,580 c. c.

Rhesus No. 77 was fed in November, 1913, with 680 c. c. from case 11, and in December, 1913, with 235 c. c. from case 11; total, 915 c. c. Rhesus No. 77 died August 4, 1915, from tuberculosis.

The principal symptoms manifested by pellagrins at the time they furnished the sputum for feeding were the following:

Case 19. Sore mouth and diarrhea; eruption on hands, elbows, and neck.

Case 20. Sore mouth and diarrhea; eruption on hands and elbows.

Case 21. Sore mouth; scaly eruption on elbows and hands.

Case 22. Sore mouth and red tongue; eruption on hands.

Case 23. Sore mouth and eruption on hands.

Case 24. Red tongue and diarrhea.

Case 25. Red tongue, sore mouth, and eruption on hands.

Case 26. Sore mouth and diarrhea; scaly eruption on arms and legs.

Case 11. Eruption on elbow and hands; burning sensation in feet; indigestion.

Case 12. Red tongue, sore mouth, and diarrhea; eruption on hands, wrists, nose, and face; burning sensation of feet.

These experiments are set forth in tabular form as follows:

TABLE No. 10.—*Feeding of sputum.*

Date of feeding.	Source of sputum.	C. c. fed.	Monkey number.	Remarks.
November, 1913	Case 19	700	9	No. 9 died June 28, 1915, from the acute effects of an injection.
February, 1914	Cases 23 and 24	1,030	9	
March, 1914	Cases 23, 24, and 12	1,900	9	
November, 1913	Case 21	350	14	No. 14 died June 23, 1915, from the acute effects of an injection.
	Case 22	300	14	
March, 1914	Case 12	1,000	14	
November, 1913	Case 25	980	16	
December, 1913	do	200	16	
March, 1914	Case 12	1,040	16	
November, 1913	Case 20	365	23	
	Case 26	300	23	
December, 1913	Case 20	115	23	
March, 1914	Case 12	800	23	
November, 1913	Case 11	680	77	No. 77 died Aug. 4, 1915. Tuberculosis.
December, 1913	do	235	77	

FEEDING OF PELLAGROUS TISSUES.

At autopsy No. 3, performed 12 hours after death, the stomach and contents, the large and small intestines and contents, pancreas, spleen, mesentery, and mesenteric glands were removed, ground in a meat grinder, placed in the ice box, and fed by tube into the empty stomachs of rhesus monkeys Nos. 1, 2, 3, 4, 5, 6, 8, and baboon 66. The feedings were made daily from October 14 until the material was exhausted, October 28, 1913. No. 2 died June 24, 1915, from the acute effects of an injection. No. 4 died April 15, 1914; autopsy showed marked congestion of brain and cord. No. 8 died February 23, 1915, from tuberculosis.

At autopsy No. 4, performed 8 hours after death, the stomach and contents, large and small intestines and contents, pancreas, spleen, portion of liver, kidney, mesentery, and mesenteric lymph glands were removed, ground in a meat grinder, placed in the ice box, and fed by tube into the empty stomachs of rhesus monkeys Nos. 1, 2, 3, 4, 5, 6, 8, 29, 31, 32, 33, 34, 35 36, 37, and baboons 65 and 66. The feedings were daily from October 29 to November 6, 1913. Nos. 2, 4, and 8 died from causes indicated above. No. 29 died November 26, 1913, from cause not apparent at autopsy. No. 31 died February, 1914, from cause not apparent at autopsy. No. 32 died June 22, 1915, from tuberculosis. No. 33 died March 7, 1915, from tuberculosis. Baboon No. 65 died June 2, 1914, from cause not apparent at autopsy.

At autopsy No. 5, performed 9 hours after death, the stomach and contents and the large and small intestines and contents were removed, ground in a meat grinder, placed in the ice box, and fed by tube into the empty stomachs of rhesus monkeys Nos. 1, 2, 3, 4, 5, 6, 8, and baboon 65. The feedings were daily from December 29, 1913, to January 3, 1914. Nos. 2, 4, 8, and 65 died from causes indicated above.

At autopsy No. 6 performed 13½ hours after death the entire contents of the buccal, thoracic, and abdominal cavities were removed, the tissues being divided only at their bony attachments. This mass of organs was ground in a meat chopper, placed in the ice box, and fed by tube into the empty stomachs of rhesus monkeys Nos. 1, 2, 3, 4, 5, 6, 8, 31, 32, 33, 34, 35, 36, 37, and baboons 65 and 66. Nos. 2, 4, 8, 32, 33, and 65 died from causes indicated above. The feedings were daily from January 21 to 28, 1914.

On January 29 the same animals were fed in the same way with the entire brain and spinal cord and portions of the ulnar and sciatic nerves from autopsy No. 6, which had been kept since January 20 in the ice box.

At autopsy No. 7 performed three hours after death the entire brain, spinal cord, and their membranes were removed, ground in a grinder, placed in the ice box, and fed by tube on February 5, 1914, into the empty stomachs of rhesus monkeys Nos. 1, 2, 3, 4, 5, 6, 8, 32, 33, 34, 36, 37, 95, 96, and baboon 64. Nos. 2, 4, 8, 32, and 33 died from causes indicated above.

The entire contents of the buccal and thoracic cavities, leaving only the denuded bony surfaces, were prepared and treated as was the nervous tissue, and fed to the same animals February 6.

The entire contents of the abdominal cavity, excepting stomach, small intestines, large intestines, and feces, but including liver, spleen, kidneys, omentum, mesentery, uterus, ovaries, lymph glands, etc., were stripped out complete, ground, and kept cool, as was the nervous tissue, and fed to the same animals on February 7 and 9.

The stomach, small intestines, and large intestines, after stripping out their contents, were ground and kept cool, as was the nervous tissue, and fed to the same animals on February 10.

At autopsy No. 8 performed eight hours after death the entire brain, spinal cord, and their membranes were removed, ground in a meat grinder, placed in the ice box, and fed on April 13, 1914, by tube into the empty stomachs of rhesus monkeys Nos. 11, 13, 17, 18, 19, 26, 27, 28, 32, 33, 34, 35, 36, 37, 53, 58, 95, 96, and baboon 65. No. 11 died July 2, 1915, from the acute effects of an injection. No. 58 died July 8 1915, from the acute effects of an injection. No. 17 died October, 1915, from cause not apparent at autopsy. Nos. 32, 33, and 65 died from causes indicated above.

These experiments are given in tabular form as follows:

TABLE No. 11.—*Feeding of pellagrous tissues.*

Date of feeding.	Source of material; autopsy.	Hours between death and collection of autopsy material.	Material used for feeding.	Monkey No.	Remarks.
1913. Oct. 14–28	No. 3	12	Stomach and contents, large intestines and contents, small intestines and contents, pancreas, spleen, mesentery, mesenteric glands.	Rhesus 1, 2, 3, 4, 5, 6, 8, and baboon 66.	No. 2 died June, 1915, due to an injection. No. 4 died April, 1914, from cause not apparent at autopsy. No. 8 died February, 1915; tuberculosis.
Oct. 29–Nov. 6	No. 4	8	Stomach and contents, large intestines and contents, small intestines and contents, pancreas, spleen, portion of liver, one kidney, mesentery, mesenteric glands.	Rhesus 1, 2, 3, 4, 5, 6, 8, 29, 31, 32, 33, 34, 35, 36, 37, and baboons 65 and 66.	No. 29 died November, 1913, from cause not apparent at autopsy. No. 31 died February, 1914, from cause not apparent at autopsy. No. 32 died June, 1915; tuberculosis. No. 33 died March, 1915; tuberculosis.
Dec. 29–Jan. 3	No. 5	9	Stomach and contents, large intestnes and contents, small intestines and contents.	Rhesus 1, 2, 3, 4, 5, 6, 8, and baboon 65.	No. 65 (baboon) died June, 1914, from cause not apparent at autopsy.
1914. Jan. 21–29	No. 6	13½	Entire contents of buccal, thoracic and abdominal cavities.	Rhesus 1, 2, 3, 4, 5, 6, 8, 31, 32, 33, 34, 35, 36, 37, and baboons 65 66.	
Jan. 29	No. 6	13½	Entire brain and spinal cord and portions of the ulnar and sciatic nerves.	do	
Feb. 5	No. 7	3	Brain, spinal cord and their membranes.	Rhesus 1, 2, 3, 4, 5, 6, 8, 32, 33, 34, 36, 37, 95, 96, and baboon 64.	
Feb. 6	No. 7		Entire contents of buccal and thoracic cavities.	do	
Feb. 7 and 9	No. 7		Entire contents of abdominal cavity except stomach, intestines, and their contents.	do	
Feb. 10	No. 7		Stomach, large and small intestines without contents.	do	
Apr. 13	No. 8	8	Brain, spinal cord and their membranes.	Rhesus 11, 13, 17, 18, 19, 26, 27, 28, 32, 33, 34, 35, 36, 37, 53, 58, 95, 96, and baboon 65.	No. 11 died July, 1915, due to an injection. No. 58 died July, 1915, due to an injection. No. 17 died October, 1915, from cause not apparent at autopsy.

FEEDING OF PELLAGROUS TISSUES AND SPOILED CORN MEAL.

At autopsy No. 8, performed eight hours after death, the entire contents of the buccal, thoracic, and abdominal cavities were removed en masse, ground in a meat grinder, placed in the ice box, and fed by tube April 14, 15, 16, and 17, 1914, into the empty stomachs of rhesus monkeys Nos. 11, 13, 17, 18, 19, 26, 27, 28, 32, 33, 34, 35, 36, 37, 53, 58, 95, 96, and baboon 65, each receiving a daily feeding consisting of 70 c. c. of tissue and 20 grams of spoiled corn meal.

Nos. 11, 17, 32, 33, 58, and 65 died from causes indicated above.

FEEDING OF FECES AND SPOILED CORN MEAL.

Diarrheal feces collected at autopsy No. 7 from all parts of the large and small intestines were kept in the ice box from February 4, 1914, the day of the autopsy, to February 11, and daily feedings. beginning February 5, were made by tube into the stomachs of rhesus monkeys Nos. 93 and 94, using for each animal at each feeding 70 c. c. of feces and 20 grams of spoiled corn meal. Rhesus No. 93 died March 29, 1915, from monkey birth.

Diarrheal feces collected fresh each day from a pellagrin who became autopsy No. 8 were mixed with spoiled corn meal and fed by tube daily into the empty stomachs of monkeys from March 11, 1914, to April 3, 1914, using for each animal at each feeding 70 c. c. of feces and 20 grams of spoiled corn meal. Fifteen such feedings were made into each of monkeys Nos. 93, 94, 1, 2, 3, and 4; three such feedings were made into Nos. 6 and 8. Nos. 2, 4, 8, and 93 died from causes indicated above.

SUMMARY.

The opinion of some workers that pellagra is a specific infectious disease, and the report by Harris, of New Orleans, of the production of pellagra in the monkey by the injection of a Berkefeld filtrate of pellagrous tissues, led the United States Public Health Service as a part of its study of pellagra to attack exhaustively the problem of the infectivity of pellagrous tissues and body fluids for the rhesus monkey.

The experiments here reported consist of a series of inoculations and feedings of pellagrous tissues and fluids into 90 rhesus monkeys, 3 baboons, and 1 Java monkey. The experiments were begun at the United States Marine Hospital, Savannah, Ga., in July, 1913; were continued through 1914, and were completed in June, 1915.

Throughout this period the experimental animals were bountifully fed and were kept under daily observation in cages in a glass-covered conservatory, located on the south side of the hospital and freely exposed to the direct rays of the sun.

The sources of the pellagrous material with which the animals were inoculated or fed were 10 autopsies and 50 living pellagrins, the protocols of which appear in Appendix I.

In all, 252 experiments were made with material collected during life or at autopsy; in 141 of these, inoculation was made by hypodermic needle; in 82, material was fed by stomach tube; in 29, feces were applied to the nasal mucosa.

With few exceptions each animal was inoculated by more than one route, with two or more kinds of material, from more than one case, and on more than one occasion.

Twenty-eight animals were each subjected to a single experiment; 19 were each subjected to 2 experiments; 17 were subjected to 3 experiments each; 19 were subjected to 4 each; 7 were subjected to 5 each; and 4 were subjected to 6 experiments each.

The material used for inoculation or feeding was disposed of as follows:

(*a*) The brain, spinal cord, and their membranes were removed at 8 autopsies, ground in a meat grinder, extracted with saline solution, filtered through gauze, and injected cerebrally, venously, and subcutaneously into 2 rhesus monkeys, cerebrally and venously into 1, cerebrally and muscularly into 2, cerebrally and peritoneally into 2, spinally and peritoneally into 4, spinally into 12, and venously into 2, and after Berkefeld filtration, were injected spinally into 4.

(*b*) The buccal, thoracic, and abdominal organs except intestines were removed at one autopsy, ground in a meat grinder, extracted with saline solution, filtered through gauze, and injected venously and subcutaneously into 7 rhesus monkeys, and after Berkefeld filtration, were injected venously into 3 rhesus monkeys.

(*c*) The intestines and fecal contents were removed at 7 autopsies, ground in a meat grinder, extracted with saline solution, squeezed through gauze, and injected venously into 7 rhesus monkeys and 1 Java monkey, and after Berkefeld filtration, were injected cerebrally, venously, and subcutaneously into 1 rhesus monkey, cerebrally and venously into 1 baboon, venously into 1 baboon, venously and subcutaneously into 10 rhesus monkeys.

(*d*) Skin showing the pellagrous lesions was removed at 5 autopsies, ground in a meat grinder, extracted with saline solution, filtered through gauze, and injected cerebrally, venously, and subcutaneously into 1 rhesus monkey, cerebrally and venously into 1 Java monkey, venously and subcutaneously into 3 rhesus monkeys, venously into 3, and after Berkefeld filtration, was injected cerebrally, venously, and subcutaneously into 2 rhesus monkeys.

(*e*) Blood drawn from 8 pellagrins was, after defibrination, injected venously into 1 rhesus monkey and spinally and muscularly into 2; after citration was injected muscularly into 3; or the mixed defibrinated and citrated blood was injected venously and peritoneally into 4 rhesus monkeys and peritoneally into 1.

(*f*) Cerebrospinal fluid collected at 5 autopsies was injected cerebrally and venously into 1 rhesus monkey and spinally into 5; or after Berkefeld filtration, was injected spinally into 10 rhesus monkeys.

(*g*) Spinal fluid collected during life from 28 pellagrins was injected without filtration immediately after collection in amounts of 5 c. c. or more intraspinally into 24 rhesus monkeys, 1 receiving 5 injections of approximately 5 c. c. each, another receiving 4 such injections, another receiving 3 injections, 16 others receiving 2 injections, and 5 others receiving only 1 injection each.

(*h*) Pericardial fluid collected at one autopsy was injected without filtration venously into 2 rhesus monkeys and after filtration was injected spinally into 2 rhesus monkeys.

(*i*) Urine from 4 pellagrins, giving a marked indican reaction, was injected after Berkefeld filtration venously into 5 rhesus monkeys, each receiving, respectively, 270 c. c., 215 c. c., 155 c. c., 105 c. c., and 90 c. c.

(*j*) Feces from 3 pellagrins with marked diarrhea were, after Berkefeld filtration, injected peritoneally into 26 rhesus monkeys in amounts from 40 to 130 c. c. each of undiluted fecal filtrate.

(*k*) Feces from 1 autopsy and from 2 pellagrins were introduced on cotton pledgets into the nasal fossæ of 29 rhesus monkeys.

(*l*) Sputum collected fresh each day from 10 spitting pellagrins was fed by stomach tube to 5 rhesus monkeys in total amounts, respectively, of 3,630 c. c., 1,650 c. c., 2,220 c. c., 1,580 c. c., and 915 c. c.

(*m*) The brain, spinal cord, and their membranes collected at 2 autopsies, after being ground, were fed by a stomach tube to 25 rhesus monkeys and 2 baboons.

(*n*) The entire contents of the buccal and thoracic cavities collected at 2 autopsies, after being ground, were fed by stomach tube to 16 rhesus monkeys and 3 baboons.

(*o*) The entire contents of the abdominal cavity collected at 4 autopsies, after being ground, were fed by stomach tube to 17 rhesus monkeys and 3 baboons.

(*p*) The entire contents of the buccal, thoracic, and abdominal cavities were removed at one autopsy, and after being ground and mixed with spoiled corn meal were fed by stomach tube to 18 rhesus monkeys and 1 baboon.

(*q*) Feces collected at one autopsy were mixed with spoiled corn meal and fed by stomach tube to 2 rhesus monkeys.

(*r*) Feces collected fresh each day from a fatal case of pellagra with diarrhea were mixed with spoiled corn meal and fed by tube daily for 15 days to 6 rhesus monkeys and daily for 3 days to 2 others.

A summary of all the individual experiments on each monkey is contained in Appendix II.

RESULTS.

Of the 94 animals here reported upon, 54 are living and 40 are dead.[1] Eighteen of the latter died of tuberculosis; 10 died of acute peritonitis following peritoneal injections; 2 died of cerebral abscess following cerebral injection; 1 died of œsophagostomum; 1 female died in labor; while 8 died from causes which could not be determined at the autopsy.

With one exception the surviving animals have shown no indications even suggesting pellagra. The exception referred to is as follows:

Rhesus No. 98 was injected intraspinally on April 14, 1914, with 6 c. c. of spinal fluid drawn from a fatal case of pellagra three days before death. This animal was again injected intraspinally on May 2, with 4 c. c. of spinal fluid drawn from another fatal case of pellagra 24 hours before death. The first change in this monkey was noted May 4, 1914, at which time the right forearm appeared slightly swollen and looked as if some of the hair was falling out. The following day the left forearm showed a similar condition. Later both forearms became entirely denuded of hair, the skin became roughened and scaly, and large cracks yielded a slight serous exudate. Over both wrists the superficial skin seemed to be denuded and the condition gave the appearance of superficial ulceration. On the posterior surface of each hand a similar condition was noticed; the knuckles were swollen and reddish and presented cracks and broken skin. On May 9 the skin was dry and scaly. The bowel movements were occasionally loose (soft). Later thick crusts on the skin came away. leaving a pale and slightly scaly surface. By June 15, 1914, the only abnormal condition present was an absence of hair over the parts affected. Later the hair returned and the animal appeared and has remained normal in every way.

In interpreting the skin manifestations of rhesus No. 98 the evidence points to their being accidental rather than to their being of a pellagrous origin. This animal was one of 24 which received spinal injections of spinal fluid collected from 28 pellagrins during life; it was one of 19 which received two or more injections of spinal fluid. Rhesus No. 99 received five injections of spinal fluid collected from five cases, two of which were fatal; rhesus No. 100 received four injections of spinal fluid collected from four cases, three of which were fatal; rhesus No. 101 received three injections of spinal fluid from three cases, one of which was fatal. No other monkey was injected with spinal fluid from the particular pellagrins who furnished the fluid for the inoculations of rhesus No. 98.

The work here reported furnishes no support for the view that pellagra is an infectious disease.

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[1] At time this report was written, December, 1915.

APPENDIX I.

SOURCE AND DISPOSAL OF INOCULATING MATERIAL.

1. CASE NOTES.

Case 1.—E. J. S., white male, age 34, was admitted to the Marine Hospital August 12, 1913, with a skin eruption affecting both forearms and elbows, with sore mouth, diarrhea, and burning sensations in the feet. His first attack was in April, 1913. He was discharged November 10, 1913.

(*a*) Blood was drawn from the median basilic vein August 26, 1913, and after defibrination was injected intravenously (8 c. c.) into rhesus 68.

Case 2.—O. H., white male, age 27, was admitted to the Marine Hospital September 25, 1913. He was mentally so disordered that no connected history was obtainable; he had to be restrained in bed. Discharged September 30; insane.

(*a*) Blood was drawn from the median basilic vein September 29, 1913, and after defibrination was injected intravenously (8½ c. c.) into rhesus 68.

Case 3.—C. N. D., white male, age 38, was admitted to the Marine Hospital May 24, 1914, with severe dermatitis on the backs of hands and wrists and on face and neck, and with diarrhea. His first attack was in March, 1914. He was discharged July 3, 1914.

(*a*) Blood was drawn from the median basilic vein June 6, 1914, and after defibrination was injected intraspinally (5 c. c.) and intramuscularly (10 c. c.) into each of rhesus monkeys 85 and 86.

(*b*) Spinal fluid was collected June 2, 1914, and injected spinally into rhesus 71, 81, and 82.

Case 4.—W. T. D., white male, age 37, was admitted to the Marine Hospital May 27, 1914, with diarrhea and erythema on the backs of hands and wrists and on the nose and forehead. His first attack was in February, 1914. He was discharged July 23, 1914.

(*a*) Blood was drawn from the median basilic vein June 6, 1914, into citrate solution, after which 10 c. c. was injected intramuscularly into each of rhesus monkeys 10, 72, and 76.

(*b*) Spinal fluid was collected June 2, 1914, and injected spinally into rhesus 26, 27, and 80.

Case 5.—A. G., colored female, age 59, was admitted to the Georgia Infirmary May 12, 1914, with erythema on the hands, arms, and neck. She died May 30, 1914.

(*a*) Twenty c. c. of blood were drawn from cases 5, 7, and 8 on May 20, 1914, each into citrate solution. The same amount was drawn at the same time from case 6 and was defibrinated. The four bloods were then mixed and the mixture was injected intraperitoneally (6 c. c.) and intravenously (6 c. c.) into each of rhesus monkeys 72, 76, 85, and 86, and intraperitoneally (10 c. c.) into rhesus 10.

Case 6.—O. J., colored female, age 34, was admitted to the Georgia Infirmary May 19, 1914, with diarrhea and an erythema affecting the hands, forearms, and neck. Her first attack was in March, 1914. She died June 22, 1914.

(*a*) Furnished blood. (See case 5.)

Case 7.—M. P., colored female, age 33, was admitted to the Georgia Infirmary May 18, 1914, with diarrhea and with erythema affecting the hands, forearms, neck, and face. Her first attack was in May, 1913. She died June 3, 1914. (See autopsy No. 10.)

(*a*) Furnished blood. (See case 5.)

Case 8.—P. T. was a colored female, age 35, admitted to the Georgia Infirmary May 9, 1914, with diarrhea and with an erythema on the hands and forearms. Her first attack was in April, 1913. She died May 27, 1914. (See autopsy No. 9.)

(*a*) Furnished blood. (See case 5.)

Case 9.—F. D. M., white male, age 20, was admitted to the Marine Hospital November 8, 1913, with a scaly eruption on the face, neck, and elbows and with sore mouth. His first attack began in October, 1913. He was discharged December 24, 1913; readmitted March 24, 1914; and again discharged June 14, 1914.

(*a*) The mixed urine of cases 9, 10, and 11 was injected between November 26 and December 8, 1913, in daily amounts of either 10 c. c. or 20 c. c. intravenously into rhesus 10, 72, and 76, and in total amounts, respectively, of 130 c. c., 155 c. c., and 155 c. c.

(*b*) The mixed urine of cases 9 and 12 was injected between April 8 and 13, 1914, in daily amounts of either 10 c. c. or 20 c. c. intravenously into rhesus monkeys 10, 76, 93, and 94, each receiving, respectively, 85 c. c., 115 c. c., 90 c. c., and 105 c. c.

Case 10.—M. P. T., white male, age 56, was admitted to the Marine Hospital December 1, 1913. His present attack began in June, 1913, with an eruption on the hands and with diarrhea. On admission his symptoms had very much subsided. He was discharged December 13, 1913.

(*a*) Furnished urine. (See case 9.)

Case 11.—J. F. B., white male, age 54, was admitted to the Marine Hospital November 4, 1913, with a scaly eruption on the elbows and backs of hands, with sore tongue, and constipation. His present attack began in September, 1913. He had attacks in 1911 and 1912. He was discharged December 24, 1913.

(*a*) Furnished urine. (See case 9.)

(*b*) Furnished 680 c. c. sputum in November, 1913, and 235 c. c. in December, 1913, for feeding rhesus 77.

Case 12.—C. R., white male, age 51, was admitted to the Marine Hospital March 7, 1914, with sore mouth, diarrhea, eruption on the neck and backs of hands, and burning sensation of the feet. His first attack was in February, 1914, and was continuous until death, April 11, 1914. (See autopsy No. 8.)

(*a*) Furnished urine. (See case 9.)

(*b*) In March, 1914, furnished sputum for feeding monkeys, 800 c. c. for No. 23, 1,040 c. c. for No. 16, 1,000 c. c. for No. 14, some for No. 9.

(*c*) Feces collected fresh each day from March 11 to April 3 were mixed with spoiled corn meal and fed to rhesus monkeys 93, 94, 1, 2, 3. 4, 6, and 8.

Case 13.—J. P., white male, age 31, was admitted to the Marine Hospital June 16, 1915, with diarrhea, red tongue, ulcers at corners of mouth, and roughened skin on the backs of both hands and on forearms. The present attack began six weeks previously with diarrhea. His first attack occurred in the spring of 1914 and was accompanied by diarrhea; there was a fall attack in 1914 characterized by an eruption on the hands, which the patient said was due to "blistering by the sun." Patient was discharged September 8, 1915.

(*a*) Feces collected morning and evening between June 17 and 23, 1915, from cases 13, 14, and 15 were after Berkefeld filtration injected intraperitoneally into 26 rhesus monkeys. (See table No. 9.)

Case 14.—C. C., colored male, age 26, was admitted to the Marine Hospital June 15, 1915, with the following symptoms: A pigmented collar 3 inches wide encircles the neck and extends downward 1 inch behind and downward 3 inches in front. The backs of both hands and all fingers present purplish blebs, and there is ulceration between the fingers. The condition extends upward for 2 inches on the lower third of the forearms. Both feet show purplish discoloration and blebs on all parts except the soles. There is red tongue, sore lips, marked ptyalism, and marked diarrhea. Patient is well nourished. His first attack was five weeks before admission. He was discharged August 18, 1915.

(*a*) Furnished feces. (See case 13.)

Case 15.—H. O. W., white male, age 44, was admitted to the Marine Hospital June 6, 1915, with marked bilateral erythema of both hands extending to a sharp line of demarcation 1 inch above the wrists. The right elbow was red. There was marked diarrhea and burning sensations in the feet. The present attack began in February, 1915, with diarrhea and eruption on the hands. In 1913 he had an eruption extending from his fingers to his shoulders, which lasted through March and April and required bandaging. He was discharged September 25, 1915.

(*a*) Furnished feces. (See case 13.)

Case 16.—C. S., colored female, age 35, was admitted to the Georgia Infirmary September 10, 1914, presenting a red tongue, foul mouth, and bad diarrhea. The backs of the hands and fronts of the wrists showed the epidermis loosely adherent covering the moist red derma. The nose showed the usual rough comedone appearance. She died September 12, 1914.

(*a*) Furnished feces at autopsy which, with feces from cases 17 and 18, were applied to the nasal fossæ of 29 monkeys. (See intranasal application of feces.)

Case 17.—A. H. D., white male, age 65, was admitted to the Marine Hospital July 27, 1914, with an erythema on the backs of the hands and about both elbows. There was no diarrhea. His first attack began about two weeks before admission. He was discharged September 30, 1914.

(*a*) Furnished feces. (See intranasal application of feces.)

Case 18.—W. L. T., white male, age 41, was admitted to the Marine Hospital August 29, 1914, with erythema of backs of hands, forearms, and lower two-thirds of arms, with sore mouth and diarrhea. His first attack was in April, 1914. He was discharged October 13, 1914, readmitted October 25, 1914, and again discharged February 1, 1915.

(*a*) Furnished feces. (See intranasal application of feces.)

Case 19.—J. S., white female, age 38, was admitted to the Savannah Hospital November 6, 1913, with sore mouth, diarrhea, scaly eruption on neck, face, and elbows, and erythema on backs of hands. The present attack began in October, 1913, and was her first. Patient was discharged February 25, 1914.

(*a*) Furnished 700 c. c. sputum in November, 1913, for feeding rhesus 9.

Case 20.—J. W., white male, age 43, was admitted to the Marine Hospital November 1, 1913, with scaly eruption on both hands and elbows, sore mouth, and uncontrollable diarrhea. The present attack began in August, 1913. His first attack was in 1910; his second was in 1912. He died at the Marine Hospital December 27, 1913. At times during his last three weeks he exhibited mental depression and excitement. (See autopsy No. 5.)

(*a*) Furnished 365 c. c. sputum in November, 1913, and 115 c. c. in December for feeding rhesus 23.

Case 21.—A. T. D., white female, age 25, was admitted to the Savannah Hospital November 8, 1913, with sore mouth and scaly eruption on backs of hands and elbows. The present attack began in September, 1913, and was continuous with her first attack, which was in June, 1913. She was discharged December 8, 1913.

(*a*) Furnished 350 c. c. sputum in November, 1913, for feeding rhesus 14.

Case 22.—F. T., colored female, age 32, was admitted to the Georgia Infirmary October 29, 1913, with very sore mouth, constipation, and scaly eruption on backs of hands and elbows. Her first attack was in May, 1913, and continued through the summer. She died at the Georgia Infirmary January 21, 1914.

(*a*) Furnished 300 c. c. sputum in November, 1913, for feeding rhesus 14.

Case 23.—J. S. E., white male, age 38, was admitted to the Marine Hospital February 2, 1914, with erythema on backs of hands and roughness on backs of elbows. His first attack was in October, 1911. This was followed by attacks in 1912 and 1913. He was discharged February 28, 1914.

(*a*) Furnished sputum in February and March, 1914, for feeding rhesus 9.

Case 24.—W. P. F., white male, age 25, was admitted to the Marine Hospital February 9, 1914, with red tongue and diarrhea. He was discharged August 16, 1914.

(*a*) Furnished sputum in February and March, 1914, for feeding rhesus 9.

Case 25.—J. H. S., white male, age 62, was admitted to the Marine Hospital October 21, 1913, with red tongue, sore mouth, and eruption on backs of hands. His present attack began in May, 1913. His first attack was in August, 1911. He was discharged July 2, 1913.

(*a*) Furnished 980 c. c. sputum in November, 1913, and 200 c. c. in December for feeding rhesus 16.

Case 26.—Mrs. K., white female, age 58, was admitted to the Savannah Hospital November 8, 1913, with a scaly eruption on the backs of the hands and forearms, with burning sensations in the feet, sore mouth, and diarrhea. Her first attack was in July, 1910, and was more or less continuous until admission. A striking feature of the case was the continuous sore mouth. She left the hospital against advice December 2, 1913.

(*a*) Furnished 300 c. c. sputum in November, 1913, for feeding rhesus 23.

Cases 29 to 51 were colored females in the State Insane Asylum at Milledgeville, Ga. Each furnished spinal fluid for spinal injection of monkeys and for the psychiatric studies of Dr. W. F. Lorenz, by whom all the tappings and spinal inoculations were made.

Case 29.—M. I. admitted with pellagra March 21, 1914. Died of same April 17, 1914.

(*a*) Furnished spinal fluid (6 c. c.) April 14, 1914, for spinal injection of rhesus 98.

Case 30.—E. D. admitted November 2, 1913. On April 13, 1914, she had pellagra and died of same May 3, 1914.

(*a*) Furnished spinal fluid (4 c. c.) May 2, 1914, for spinal injection of rhesus 98.

Case 31.—E. H. showed red tongue, diarrhea, and eruption on hands and feet April 13, 1914.

(*a*) Furnished spinal fluid (6 c. c.) April 14, 1914, for spinal injection of rhesus 99.

Case 32.—B. A. admitted August 19, 1913; had pellagra April 14, 1914, and died of same June 22, 1914.

(*a*) Furnished spinal fluid (5 c. c.) May 2, 1914, for spinal injection of rhesus 99.

Case 33.—J. C. admitted September 23, 1913. Developed pellagra about March 20, 1914, and died of same May 20, 1914.

(*a*) Furnished spinal fluid (4 c. c.) May 7, 1914, for spinal injection of rhesus 99.

Case 34.—R. B. On May 13, 1914, she had sore mouth, diarrhea, vaginitis, and extensive moist eruption over hands and feet. On August 8, 1914. the mouth was normal, the diarrhea had ceased, and the eruption had disappeared.

(*a*) Furnished spinal fluid (7 c. c.) May 19, 1914, for spinal injection of rhesus 99 and 6 c. c. for 109.

Case 35.—M. B. On May 20, 1914, she had a red tongue, diarrhea, and eruption around eyes.

(*a*) Furnished spinal fluid (5 c. c.) May 30, 1914, for spinal injection of rhesus 99 and 5 c. c. for rhesus 109.

Case 36.—W. B. admitted April 15, 1914, with pellagra and died of same May 3, 1914.

(*a*) Furnished spinal fluid (6 c. c.) April 20, 1914, for spinal injection of rhesus 100.

Case 37.—E. B. On January 1, 1914, she had red tongue, diarrhea, and moist eruption on hands and feet. She had a previous attack in November, 1911. She died June 26, 1914.

(*a*) Furnished spinal fluid (4 c. c.) May 2, 1914, for spinal injection of rhesus 100.

Case 38.—K. H. On May 20, 1914, she had red tongue, diarrhea, and moist eruption on backs of hands and feet. On August 18, 1914, the diarrhea had stopped, the tongue was normal, and the feet were well.

(*a*) Furnished spinal fluid (6 c. c.) May 19, 1914, for spinal injection of rhesus 100 and 5 c. c. for 101.

Case 39.—L. W., admitted May 5, 1914, with pellagra and died of same June 19, 1914.

(*a*) Furnished spinal fluid (5 c. c.) May 30, 1914, for spinal injection of rhesus 100 and 5 c. c. for 107.

Case 40.—B. G., admitted March 2, 1914, with pellagra and died of same April 24, 1914.

(*a*) Furnished spinal fluid (8 c. c.) April 17, 1914, for spinal injection of rhesus 101.

Case 41.—J. W. On May 9, 1914, she had a very red tongue, diarrhea, and eruption on backs of hands. On August 8, 1914, all symptoms had practically disappeared.

(*a*) Furnished spinal fluid (5 c. c.) May 19, 1914, for spinal injection of rhesus 107 and 5 c. c. for 108.

Case 42.—M. A. On May 21, 1914, she had an eruption on the hands and around the eyes. She had a previous attack May 27, 1913.

(*a*) Furnished spinal fluid (5 c. c.) May 30, 1914, for spinal injection of rhesus 108 and 5 c. c. for 109. Furnished spinal fluid (5 c. c.) July 10, 1914, for spinal injection of rhesus 105.

Case 43.—M. P. On May 7, 1914, she had sore mouth, diarrhea, and eruption on hands and feet.

(*a*) Furnished spinal fluid (9 c. c.) June 12, 1914, for spinal injection of rhesus 102.

Case 44.—E. R. On July 25, 1914, she had sore mouth, diarrhea, and eruption on hands and feet.

(*a*) Furnished spinal fluid (5 c. c.) July 10, 1914, for spinal injection of rhesus 102 and 5 c. c. for 104.

Case 45.—C. McM. On May 3, 1914, she had sore mouth, diarrhea, and eruption on hands, wrists, and feet.

(*a*) Furnished spinal fluid (8 c. c.) June 12, 1914, for spinal injection of rhesus 103.

Case 46.—C. H. On July 24, 1914, she had sore mouth and eruption on hands, forearm, and feet.

(*a*) Furnished spinal fluid (5 c. c.) July 10, 1914, for spinal injection of rhesus 103.

Case 47.—E. V. On May 13, 1914, had sore mouth, diarrhea, and eruption.

(*a*) Furnished spinal fluid (8 c. c.) June 12, 1914, for spinal injection of rhesus 104.

Case 48.—J. B. On May 8, 1914, she had sore mouth, diarrhea, and eruption on hands and feet.

(*a*) Furnished spinal fluid (6 c. c.) June 12, 1914, for spinal injection of rhesus 105.

Case 49.—K. McD. On May 3, 1914, she had sore mouth, diarrhea, and eruption on hands, forearms, feet, and legs.

(*a*) Furnished spinal fluid (7 c. c.) June 12, 1914, for spinal injection of rhesus 106.

Case 50.—K. A. C. On July 27, 1914, she had sore mouth and eruption on hands and feet.

(*a*) Furnished spinal fluid (5 c. c.) July 10, 1914, for spinal injection of rhesus 106.

Case 51.—R. P. On March 13, 1914, she had sore mouth, diarrhea, and eruption on hands and feet.

(*a*) Furnished spinal fluid (8 c. c.) June 12, 1914, for spinal injection of rhesus 110.

Case 52.—W. H. B., white male, age 53, admitted to the Marine Hospital April 22, 1914, with erythema on backs of hands and fronts of wrists, sore mouth, and diarrhea. The present attack began in March, 1914. His first attack was in January, 1913. Patient was discharged May 22, 1914.

(*a*) Furnished spinal fluid May 13, 1914, for spinal injection (5 c. c. each) of rhesus 19, 28, and 58.

Case 53.—B. B., white, male, age 21, admitted to the Marine Hospital November 11, 1913, with eruption on hands, face, and neck, and with sore mouth, and diarrhea. The present attack began in September, 1913. His first attack was in October, 1912. Patient was discharged December 17, 1913. He was readmitted April 1, 1914, with erythema on the face and hands. On May 7, 1914, he became noisy and violent, and had to be restrained. He was discharged on his own request May 16, 1914. It was later learned that he had died.

(*a*) Furnished spinal fluid May 13, 1914, for spinal injection (5 c. c. each) of rhesus 26, 27, 80, and 84.

Case 54.—J. W., white, male, age 56, was admitted to the Marine Hospital April 25, 1914, with erythema of hands and wrists, sore mouth, and diarrhea. The present attack was his first and began in April, 1914. He was discharged September 9, 1914.

(*a*) Furnished spinal fluid May 13, 1914, for spinal injection (5 c. c. each) of rhesus 71, 73, 81, and 82.

II. AUTOPSY NOTES.

Autopsy No. 1.—M. W., died at Savannah, Ga., July 29, 1913, at 3 p. m., autopsy July 29 at 6 p. m., injection of animals was begun July 30 at 6 p. m. At autopsy there was a desquamation or peeling of the dorsum of both hands and feet and of both elbows and knees. The skin lesions also involved the back of neck, the vulva, and buttocks. There was seborrhea of the face and redness of the tongue. This was a marked case of the "wet type" of the disease.

Patient was a colored female, 35 years of age, married, and had two children. Her first attack of pellagra occurred in April, 1913.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; cerebrally, venously, and subcutaneously into rhesus 51 and 52.

(*b*) Injection of intestines and contents.

Berkefeld filtrate; cerebrally, venously, and subcutaneously into rhesus 53.

(*c*) Injection of skin.

Gauze filtrate; cerebrally, venously, and subcutaneously into rhesus 54.

Autopsy No. 2.—S. S., died at the State insane asylum, Columbia, S. C., August 17, 1913, at 8 p. m., autopsy August 17 at 9 p. m., injection of animals was begun August 18 at 6 p. m. The only skin lesion at death was a thickening and pigmentation of a triangular area on the flexor surface of each wrist and on the elbows. The patient was an insane colored female, age 35.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; cerebrally and venously into rhesus 57.

(*b*) Injection of intestines and contents.

Gauze filtrate; venously into Java 63.

Berkefeld filtrate; cerebrally and venously into baboon 64. Venously into baboon 66.

(*c*) Injection of skin.

Gauze filtrate; cerebrally and venously into Java 59.

Berkefeld filtrate; cerebrally, venously, and subcutaneously into rhesus 61 and 62.

(*d*) Injection of cerebrospinal fluid collected at autopsy. Not filtered; cerebrally and venously into rhesus 58.

Autopsy No. 3.—R. H. died at the Georgia Infirmary October 12, 1913, at 3 a. m.; autopsy October 12 at 3 p. m.; injection of animals was begun October 13 at 5 p. m. The body showed marked skin lesions involving the forearms, dorsum of hands, sacral region, and vulva.

The patient was a mulatto female, 14 years of age, single. Her first attack of the disease was in February, 1913. She was admitted to the Georgia Infirmary October 5, 1913.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; venously into rhesus 19.

(*b*) Injection of intestines and contents.

Gauze filtrate; venously into rhesus 21.

(*c*) Injection of skin.

Gauze filtrate; venously into rhesus 17 and 18.

(*d*, Table No. 11) Feeding of stomach and contents, large intestine and contents, small intestines and contents, pancreas, spleen, mesentery and mesenteric glands to rhesus monkeys 1, 2, 3, 4, 5, 6, 8, and baboon 66.

Autopsy No. 4.—D. S. died at the Savannah Hospital October 28, 1913, at 3 a. m.; autopsy October 28, at 11 a. m. The injection of animals with cerebrospinal fluid was done October 28 at 6 p. m. The injections of tissues were begun October 29.

The patient was a white female, 33 years of age, married. Her first attack was in September, 1913. On admission to the hospital, three days before death, the patient had a very sore mouth, erythema on hands, elbows, forearms, about vulva and anus, and had a diarrhea. This was regarded as a case of typhoid pellagra.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; spinally into rhesus 41; venously into rhesus 49.

(*b*) Injection of intestines and contents.

Gauze filtrate; venously into rhesus 25, 45, and 47.

(*c*) Injection of skin.

Gauze filtrate; venously and subcutaneously into rhesus 38, 39, and 40.

(*d*) Injection of cerebrospinal fluid collected at autopsy. Not filtered; spinally into rhesus 26, 27, 28, and 58.

(*e*, Table No. 11) Feeding of stomach and contents, large intestine and contents, small intestines and contents, pancreas, spleen, portion of liver, one kidney, mesentery and mesenteric glands to rhesus monkeys 1, 2, 3, 4, 5, 6, 8, 29, 31, 32, 33, 34, 35, 36, 37, and baboons 65 and 66.

Autopsy No. 5.—J. W. died at the Marine Hospital December 27, 1913, at 2 p. m.; autopsy nine hours after death.

Patient was a white male, age 43. Previous attacks were in 1910 and 1912; present attack began in August, 1913. He was admitted to the hospital November 1, 1913, with scaly eruption on both hands and elbows, sore mouth, and uncontrollable diarrhea. At times during his last three weeks he exhibited mental depression and excitement.

For disposal of autopsy material, see Table No. 11. Feeding between December 29 and January 3 of stomach and contents, large intestines and contents, and small intestines and contents to rhesus monkeys 1, 2, 3, 4, 5, 6, 8, and baboon 65.

Autopsy No. 6.—T. A. died at the Georgia Infirmary January 20, 1914, at 12.30 a. m.; autopsy, January 20, at 2 p. m. The injection of animals with pericardial fluid and cerebrospinal fluid was done January 20; injections with tissues were started January 21. The body showed skin lesions which involved the back of right hand and one elbow.

Patient was a colored male, age 25, married; admitted to hospital November 15, 1913, for diarrhea, which persisted until death. Marked skin lesions involving the back of right hand and elbow appeared December 25, 1913.

For disposal of autopsy material see following headings:

(*a*) Brain, spinal cord, and their membranes.

Berkefeld filtrate; spinally into rhesus 84.

(*b*) Injection of intestines and contents.

Gauze filtrate; venously into rhesus 85 and 86.

(*c*) Injection of skin.

Gauze filtrate; venously into rhesus 87.

(*d*) Injection of cerebrospinal fluid collected at autopsy. Not filtered; spinally into rhesus 80.

(*e*) Injection of pericardial fluid.

Not filtered; venously (10 c. c. daily for five days) into each of rhesus 81 and 82.

Berkefeld filtrate; spinally into rhesus 71 and 73.

(*f*, Table No. 11.) Feeding between January 21 and 29, 1914, of entire contents of buccal, thoracic, and abdominal cavities into rhesus monkeys 1, 2, 3, 4 5, 6, 8, 31, 32, 33, 34, 35, 36, 37, and baboons 65 and 66.

Autopsy No. 7.—M. S. died at the Savannah Hospital February 4, 1914, at 9 a. m.; autopsy February 4 at noon; injection of animals was begun February 4 at 5 p. m. The body showed an erythema of the neck, forearms, elbows, and dorsal surfaces of the feet.

Patient was a white female, age 30, single. She had had an attack of pellagra each year since 1906. The present attack began in April, 1913, and was characterized, on admission to hospital in December, 1913, by an eruption on the face, hands, arms, neck, and feet and by sore mouth and diarrhea.

For disposal of autopsy material see following headings:

(*a*) Injection of intestines and contents.

Gauze filtrate; venously into rhesus 91.

(*b*) Injection of cerebrospinal fluid collected at autopsy.

Berkefeld filtrate; spinally into rhesus 26, 27, 28, and 58.

(*c*, Table No. 11.) Feeding on February 5 of brain, spinal cord, and their membranes to rhesus monkeys 1, 2, 3, 4, 5, 6, 8, 32, 33, 34, 36, 37, 95, 96, and baboon 64; feeding on February 6 of entire contents of buccal and thoracic cavities to the same monkeys; feeding on February 7 and 9 of entire contents of abdominal cavity, except stomach, intestines, and their contents, to the same monkeys; feeding on February 10 of stomach, large and small intestines without their contents to the same monkeys.

(*d*) Feces collected from large and small intestines and mixed with spoiled corn meal were fed daily from February 5 to February 11 to rhesus monkeys 93 and 94.

Autopsy No. 8.—C. R. died at the Marine Hospital April 11, 1914, at 2 a. m.; autopsy April 11 at 10 a. m.; injection of animals with tissues was begun April 11 at 6 p. m. The body showed marked wet lesions of both hands and wrists, sore mouth, and diarrhea.

Patient was a white male, age 51; admitted to Marine Hospital March 7, 1914. His first attack began in February, 1914, and was continuous until death. It was manifested by red tongue, sore mouth, diarrhea, eruption on hands, wrists, nose, and face, and burning sensations of feet.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; spinally into rhesus 1, 2, 3, 5, 6, 25, 38, 45, 49, 61, and 62.

Berkefeld filtrate; spinally into rhesus 26, 38, and 39.

(*b*) Injection of buccal, thoracic, and abdominal organs, except intestines.

Gauze filtrate; venously and subcutaneously into rhesus 32, 33, 34, 41, 45, 47, and 49.

Berkefeld filtrate; venously into rhesus 27, 28, and 58.

(*c*) Injection of intestines and contents.

Berkefeld filtrate; venously and subcutaneously into rhesus 1, 2, 3, 5, 6, 36, 37, 39, 40, and 62.

(*d*) Injection of cerebrospinal fluid collected at autopsy.

Berkefeld filtrate; spinally into rhesus 32, 33, 34, 35, 36, and 37.

(*e*, Table No. 11.) Feeding on April 13 of the brain, spinal cord, and their membranes to rhesus monkeys 11, 13, 17, 18, 19, 26, 27, 28, 32, 33, 34, 35, 36, 37, 53, 58, 95, 96, and baboon 65.

(*f*) Feeding on April 14, 15, 16, and 17 of the entire contents of the buccal, thoracic, and abdominal cavities mixed with spoiled corn meal to rhesus monkeys 11, 13, 17, 18, 19, 26, 27, 28, 32, 33, 34, 35, 36, 37, 53, 58, 95, 96, and baboon 65.

Autopsy No. 9.—P. T. died at the Georgia Infirmary May 27, 1914, at 6 a. m.; autopsy May 27 at 11 a. m.; animals injected May 27 at 5 p. m. At autopsy the epidermis was absent or loose in a bleblike condition on both hands, both wrists, both elbows, and both feet. The tongue was red at the margin and the soft palate and pharynx were red and ulcerated. The body was well nourished. This was a marked "wet case."

Patient was a colored female, age 30. Her first attack was in April, 1913. Present attack began in February, 1914, and was manifested, on admission May 9, by erythema of hands and neck, and diarrhea.

For disposal of autopsy material see following headings:

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; spinally and peritoneally into rhesus 114, 115, 116, and 121.

Cerebrally and muscularly into rhesus 119.

Cerebrally and peritoneally into rhesus 120.

Autopsy No. 10.—M. P. died at the Georgia Infirmary June 3, 1914, at 1 a. m.; autopsy June 3 at 10 a. m.; animals injected June 3 at 3 p. m. At autopsy the epidermis was absent or exfoliating in large pieces, leaving reddened moist dermis in the following locations: Back of all fingers, backs and front of both wrists, backs of both forearms halfway to elbows, backs of both elbows, between nates, and about vulva. There had been marked lesions on all eyelids and about the chin. Mouth was in a very bad condition. The body was well nourished.

Patient was a colored female, age 35. Her first attack was in May, 1913. Present attack began in May, 1914. Admitted to Georgia Infirmary May 18, 1914.

For disposal of autopsy material see following headings.

(*a*) Injection of brain, spinal cord, and their membranes.

Gauze filtrate; cerebrally and peritoneally into rhesus 123. Cerebrally and muscularly into rhesus 117.

APPENDIX II.

SUMMARY OF INDIVIDUAL EXPERIMENTS MADE UPON EACH MONKEY.

Rhesus No. 1.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
1915. June 17 to 23, intraperitoneally (90 c. c.) Berkefeld filtrate of feces.

Rhesus No. 2.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
1915. June 17 to 20, intraperitoneally (60 c. c.) Berkefeld filtrate of feces.
Died June 24, 1915; few adhesions between loops of intestines.

Rhesus No. 3.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 28, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
1915. June 17 to 23, intraperitoneally (110 c. c.) Berkefeld filtrate of feces.

Rhesus No. 4.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 28, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
Died April 15, 1914; marked congestion of brain and spinal cord.

Rhesus No. 5.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 28, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.

Rhesus No. 6.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.

Rhesus No. 8.

1913. October 14 to 28, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
December 29 to January 3, fed with tissues from autopsy No. 5.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
September 18, intranasal application of feces.
Died February 23, 1915; tuberculosis.

Rhesus No. 9.

1913. November 9 to 25, fed with sputum (700 c. c.).
1914. February and March, fed with sputum (2,970 c. c.).
September 18, intranasal application of feces.
1915. June 17 to 23, intraperitoneally (90 c. c.) Berkefeld filtrate of feces.
Died June 28, 1915; injection of esophagus, stomach, intestines, and kidneys. Gall bladder large and distended.

Rhesus No. 10.

1913. November 29 to December 8, intravenously (130 c. c.) urine.
1914. April 8 to 13, intravenously (85 c. c.) urine.
June 6, intramuscularly (10 c. c.) blood.
1915. June 17 and 18, intraperitoneally (30 c. c.) Berkefeld filtrate of feces.
Died June 19, 1915; omentum injected.

Rhesus No. 11.

1915. June 17 to 20, intraperitoneally (50 c. c.) Berkefeld filtrate of feces.
Died July 2, 1915; four superficial small abcesses of liver.

Rhesus No. 13.

1915. June 17 to 23, intraperitoneally (110 c. c.) Berkefeld filtrate of feces.

Rhesus No. 14.

1913. November 9 to 25, fed with sputum (650 c. c.).
1914. March 7 to 31, fed with sputum (1,000 c. c.).
September 18, intranasal application of feces.
1915. June 17 to 23, intraperitoneally (90 c. c.) Berkefeld filtrate of feces.
Died June 23, 1915; injection and adhesions of all abdominal organs.

Rhesus No. 16.

1913. November 13 to 26, fed with sputum (910 c. c.).
December 2 to 8, fed with sputum (190 c. c.).
1914. March 17 to 31, fed with sputum (1,100 c. c.).

Rhesus No. 17.

1913. October 13, intravenously (1 c. c.) gauze filtrate of skin, autopsy No. 3.
1915. June 17 to 23, intraperitoneally (120 c. c.) Berkefeld filtrate of feces.
Died October 26, 1915; cause of death not apparent at autopsy.

Rhesus No. 18.

1913. October 13 to 17, intravenously (1 c. c. daily) gauze filtrate of skin, autopsy No. 3.

Rhesus No. 19.

1913. October 13 to 16, intravenously (½ c. c. daily) gauze filtrate of brain and spinal cord, autopsy No. 3.
1914. May 13, intraspinally (5 c. c.) spinal fluid from patient W. H. B.

Rhesus No. 21.

1913. October 13, intravenously (1 c. c.) gauze filtrate intestines and contents, autopsy No. 3.
Died March 16, 1914; tuberculosis.

Rhesus No. 23.

1913. November 13 to 25, fed with sputum (700 c. c.).
December 2 to 8, fed with sputum (100 c. c.).
1914. March 17 to 31, fed with sputum (780 c. c.).

Rhesus No. 24.

1915. June 20 to 23, intraperitoneally (80 c. c.) Berkefeld filtrate feces.
Died July 21, 1915; tuberculosis.

Rhesus No. 25.

1913. November 4 and 8, intravenously (1 c. c. each time) gauze filtrate intestines and contents autopsy No. 4.
Died February 18, 1915; tuberculosis.

Rhesus No. 26.

1913. October 28, intraspinally (1 c. c.) cerebrospinal fluid autopsy No. 4.
1914. February 4, intraspinally (4 c. c.) cerebrospinal fluid autopsy No. 7.
May 13, intraspinally (5 c. c.) spinal fluid patient B. B.
June 2, intraspinally (9 c. c.) spinal fluid patient W. T. D.

Rhesus No. 27.

1913. October 28, intraspinally (2 c. c.) cerebrospinal fluid autopsy No. 4.
1914. February 4, intraspinally (5 c. c.) cerebrospinal fluid autopsy No. 7.
May 13, intraspinally (5 c. c.) spinal fluid patient B. B.
June 2, intraspinally (9 c. c.) spinal fluid patient W. T. D.

Rhesus No. 28.

1913. October 28, intraspinally (3 c. c.) cerebrospinal fluid from autopsy No. 4.
1914. February 4, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 7.
May 15, intraspinally (5 c. c.) spinal fluid from patient W. H. B.
September 19, intranasal application of feces.

Rhesus No. 29.

1913. October 29 to November 6, fed with tissues from autopsy No. 4.
Died November 26, 1913; autopsy failed to reveal cause of death.

Rhesus No. 31.

1913. October 29 to November 3, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
Died February 2, 1914; autopsy failed to reveal cause of death.

Rhesus No. 32.

1913. October 29 to November 3, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinal injection (5 c. c.) cerebrospinal fluid autopsy No. 8.
Died June 22, 1915; tuberculosis.

Rhesus No. 33.

1913. October 29 to November 3, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 8.
Died March 7, 1915; tuberculosis.

Rhesus No. 34.

1913. October 29 to 31, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 8.

Rhesus No. 35.

1913. October 29 to November 1, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 8.

Rhesus No. 36.

1913. October 29 to November 3, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 8.

Rhesus No. 37.

1913. October 29 to November 4, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.
February 5 to 10, fed with tissues from autopsy No. 7.
April 11, intraspinally (5 c. c.) cerebrospinal fluid from autopsy No. 8.
1915. June 21 to 23, intraperitoneally (60 c. c.) Berkefeld filtrate of feces.

Rhesus No. 38.

1913. October 29, intravenously (2 c. c.), subcutaneously (1 c. c.) gauze filtrate skin autopsy No. 4.
1914. September 18, intranasal application feces.
Died February 19, 1915; tuberculosis.

Rhesus No. 39.

1913. October 29, intravenously (2 c. c.), subcutaneously (1 c. c.) gauze filtrate skin autopsy No. 4.
Died July 31, 1915; cause of death not apparent at autopsy.

Rhesus No. 40.

1913. October 29, intravenously (2 c. c.), subcutaneously (1 c. c.) gauze filtrate skin autopsy No. 4.

Rhesus No. 41.

1913. October 29, intraspinally (1 c. c.) gauze filtrate nervous tissue autopsy No. 4.

Rhesus No. 43.

1913. October 29, intraspinally (1.3 c. c.) gauze filtrate nervous tissue autopsy No. 4.
Died January 14, 1914; tuberculosis.

Rhesus No. 45.

1913. October 29, intravenously (2 c. c.) gauze filtrate intestines and contents autopsy No. 4.

Rhesus No. 47.

1913. October 29, intravenously (2 c. c.) gauze filtrate intestines and contents autopsy No. 4.

Rhesus No. 49.

1913. October 30, intravenously (2 c. c.) gauze filtrate brain cord and membranes autopsy No. 4.

Rhesus No. 50.

1913. October 30, intravenously (1 c. c.) gauze filtrate brain cord and membranes autopsy No. 4.
Died January 21, 1914; tuberculosis.

Rhesus No. 51.

1913. July 30, intracerebrally (1 c. c.), intravenously (3 c. c.), subcutaneously (4 c. c.), gauze filtrate brain cord and membranes autopsy No. 1.
Died June 12, 1914; tuberculosis.

Rhesus No. 52.

1913. July 30, intracerebrally (1 c. c.), intravenously (5 c. c.), subcutaneously (4 c. c.), gauze filtrate brain cord and membranes autopsy No. 1.
Died August 31, 1913; cerebral abscess.

Rhesus No. 53.

1913. July 30, intracerebrally (1 c. c.), intravenously (12 c. c.), subcutaneously (3 c. c.), Berkefeld filtrate intestines and contents autopsy No. 1.

Rhesus No. 54.

1913. July 30, intracerebrally (1 c. c.), intravenously (5 c. c.), subcutaneously (3 c. c.), gauze filtrate skin autopsy No. 1.

Died February 11, 1914; tuberculosis.

Rhesus No. 57.

1913. August 18, intracerebrally (1 c. c.), intravenously (5 c. c.), gauze filtrate brain cord and membrane autopsy No. 2.

Died October 27, 1913; cerebral abscess.

Rhesus No. 58.

1913. August 18, intracerebrally (1 c. c.), intravenously (5 c. c.), cerebrospinal fluid autopsy No. 2.

October 28, intraspinally (4.5 c. c.) cerebrospinal fluid autopsy No. 4.

1914. February 4, intraspinally (4 c. c.) Berkefeld filtrate cerebrospinal fluid autopsy No. 7.

May 13, intraspinally (5 c. c.) cerebrospinal fluid patient W. H. B.

1915. June 17 to 23, intraperitoneally (90 c. c.) Berkefeld filtrate of feces.

Died July 8, 1915; abscess in abdominal wall.

Java No. 59.

1913. August 18, intracerebrally (1 c. c.), intravenously (4 c. c.), gauze filtrate skin autopsy No. 2.

Died October 9, 1913, from oesophogostomum.

Rhesus No. 61.

1913. August 18, intracerebrally (1 c. c.), intravenously (9 c. c.), subcutaneously (4 c. c.), Berkefeld filtrate skin autopsy No. 2.

Rhesus No. 62.

1913. August 18, intracerebrally (1 c. c.), intravenously (10 c. c.), subcutaneously (6 c. c.), Berkefeld filtrate skin autopsy No. 2.

Baboon No. 64.

1913. August 18, intracerebrally (1 c. c.), intravenously (7 c. c.), Berkefeld filtrate intestines and contents autopsy No. 2.

1914. February 5 to 10, fed with tissues from autopsy No. 7.

Baboon No. 65.

1913. October 29 to November 6, fed with tissues from autopsy No. 4.

December 29 to January 3, fed with tissues from autopsy No. 5.

1914. January 21 to 29, fed with tissues from autopsy No. 6.

April 13 to 17, fed with tissues from autopsy No. 8.

Died June 2, 1914; autopsy failed to reveal cause of death.

Baboon No. 66.

1913. August 18 to September 17, intravenously (15 c. c.) Berkefeld filtrate feces autopsy No. 2.
October 14 to 22, fed with tissues from autopsy No. 3.
October 29 to November 6, fed with tissues from autopsy No. 4.
1914. January 21 to 29, fed with tissues from autopsy No. 6.

Rhesus No. 68.

1913. August 25, intravenously (2 c. c.) blood.
August 26, intravenously (8 c. c.) blood.
September 29, intravenously (8½ c. c.) blood.
Died January 8, 1914; tuberculosis.

Rhesus No. 71.

1914. January 23, intraspinally (5 c. c.) pericardial fluid autopsy No. 6.
May 13, intraspinally (5 c. c.) spinal fluid patient J. W.
June 2, intraspinally (9 c. c.) spinal fluid patient C. N. D.

Rhesus No. 72.

1913. November 26 to December 8, intravenously (155 c. c.) Berkefeld filtrate of urine.
1914. June 6, intramuscularly (10 c. c.) blood patient W. T. D.
September 19, intranasal application feces.

Rhesus No. 73.

1914. January 23 and 26, intraspinally (5 c. c., 5 c. c.) pericardial fluid autopsy No. 6.
May 13, intraspinously (5 c. c.) spinal fluid patient J. W.

Rhesus No. 76.

1913. November 26 to December 8, intravenously (155 c. c.) Berkefeld filtrate of urine.
1914. April 8 to 13, intravenously (115 c. c.) Berkefeld filtrate of urine.
June 6, intramuscularly (10 c. c.) blood of patient W. T. D.
September 18, intranasal application feces.
Died July 26, 1915; tuberculosis.

Rhesus No. 77.

1913. November 14 to 26, fed with sputum (680 c. c.).
December 2 to 8, fed with sputum (235 c. c.).
1915. June 20 to 22, intraperitoneally (60 c. c.) Berkefeld filtrate of feces.
Died August 4, 1915; tuberculosis.

Rhesus No. 78.

1915. June 22 and 23, intraperitoneal injection (40 c. c.) Berkefeld filtrate feces.

Rhesus No. 80.

1914. January 14, intraspinally (4.5 c. c.) cerebrospinal fluid autopsy No. 6.
May 13, intraspinally (5 c. c.) spinal fluid patient B. B.
June 2, intraspinally (9 c. c.) spinal fluid patient W. T. D.

Rhesus No. 81.

1914. January 20 to 26, intravenously (10 c. c. daily) pericardial fluid autopsy No. 6.
May 13, intraspinally (5 c. c.) spinal fluid patient J. W.
June 2, intraspinally (9 c. c.) spinal fluid patient C. N. D.
September 18, intranasal application feces.

Rhesus No. 82.

1914. January 20 to 26, intravenously (10 c. c. daily) pericardial fluid autopsy No. 6.
May 13, intraspinally (5 c. c.) spinal fluid patient J. W.
June 2, intraspinally (9 c. c.) spinal fluid patient C. N. D.
September 18, intranasal application feces.
1915. June 17 to 21, intraperitoneally (90 c. c.) Berkefeld filtrate feces.
Died July 2, 1915; marked adhesions affecting intestines and omentum.

Rhesus No. 84.

1914. January 21 and 22, intraspinally (5 c. c. each day) Berkefeld filtrate brain cord and membranes autopsy No. 6.
May 13, intraspinally (5 c. c.) spinal fluid patient B. B.
Died May 1, 1915; tuberculosis.

Rhesus No. 85.

1914. January 21 to 22, intravenously (1 c. c., 2 c. c.) gauze filtrate intestines and contents autopsy No. 6.
May 20, intravenously (6 c. c.), intraperitoneally (6 c. c.) mixed blood.
June 6, intraspinally (5 c. c.), intramuscularly (10 c. c.) blood patient C. N. D.

Rhesus No. 86.

1914. January 21–22, intravenously (2 c. c., 3 c. c.) gauze filtrate intestines and contents autopsy No. 6.
May 20, intravenously (6 c. c.), intraperitoneally (6 c. c.) mixed blood.
June 6, intraspinally (5 c. c.), intramuscularly (10 c. c.) blood patient C. N. D.

Rhesus No. 87.

1914. January 21, intravenously (2 c. c.) gauze filtrate skin autopsy No. 6.

Rhesus No. 91.

1914. February 4, intravenously (1 c. c.) gauze filtrate intestines and contents autopsy No. 7.
1915. June 21 to 23, intraperitoneally (60 c. c.) Berkefeld filtrate feces.

Rhesus No. 93.

1914. February 5 to 11, fed feces and spoiled corn meal.
April 8 to 13, intravenously (90 c. c.) urine.
Died March 29, 1915; monkey birth.

Rhesus No. 94.

1914. February 5 to 11, fed feces and spoiled corn meal.
April 8 to 13, intravenously (105 c. c.) urine.

Rhesus No. 95.

1914. February 5 to 11, fed with tissues from autopsy No. 7.

Rhesus No. 96.

1914. February 5 to 10, fed with tissues from autopsy No. 7.

Rhesus No. 97.

1914. February 17 to 18, fed amebic stool of a nonpellagrin (150 c. c. and 100 c. c.)
1915. June 17 to 23, intraperitoneally (130 c. c.) Berkefeld filtrate feces.
Died October 5, 1915; tuberculosis.

Rhesus No. 98.

1914. April 14, intraspinally (6 c. c.) spinal fluid M. T.
May 2, intraspinally (4 c. c.) spinal fluid E. D.
September 18, intranasal application feces.
1915. June 18 to 22, intraperitoneally (100 c. c.) Berkefeld filtrate feces.

Rhesus No. 99.

1914. April 14, intraspinally (6 c. c.) spinal fluid E. H.
May 2, intraspinally (5 c. c.) spinal fluid B. A.
May 7, intraspinally (4 c. c.) spinal fluid I. C.
May 19, intraspinally (7 c. c.) spinal fluid R. B.
May 30, intraspinally (5 c. c.) spinal fluid M. B.
September 18, intranasal application feces.
1915. June 17 to 23, intraperitoneally (130 c. c.) Berkefeld filtrate feces.

Rhesus No. 100.

1914. April 20, intraspinally (6 c. c.) spinal fluid W. B.
May 2, intraspinally (4 c. c.) spinal fluid E. B.
May 19, intraspinally (6 c. c.) spinal fluid K. H.
May 30, intraspinally (5 c. c.) spinal fluid J. W.
September 18, intranasal application feces.
Died December 18, 1914; tuberculosis.

Rhesus No. 101.

1914. April 17, intraspinally (8 c. c.) spinal fluid B. G.
May 19, intraspinally (5 c. c.) spinal fluid K. H.
May 30,, intraspinally (5 c. c.) spinal fluid M. B.
September 18, intranasal application feces.
1915. June 17 to 23, intraperitoneally (110 c. c.) Berkefeld filtrate feces.
Died June 27, 1915; adhesions between intestines and between intestines and omentum.

Rhesus No. 102.

1914. June 12, intraspinally (9 c. c.) spinal fluid M. P.
July 10, intraspinally (5 c. c.) spinal fluid E. R.

Rhesus No. 103.

1914. June 12, intraspinally (8 c. c.) spinal fluid C. McM.
July 10, intraspinally (5 c. c.) spinal fluid C. H.
September 18, intranasal application feces.

Rhesus No. 104.

1914. June 12, intraspinally (8 c. c.) spinal fluid E. V.
July 10, intraspinally (5 c. c.) spinal fluid E. R.
September 18, intranasal application feces.

Rhesus No. 105.

1914. June 12, intraspinally (6 c. c.) spinal fluid J. B.
July 10, intraspinally (5 c. c.) spinal fluid M. A.
September 18, intranasal application feces.
Died October 13, 1915, cause of death not apparent at autopsy.

Rhesus No. 106.

1914. June 12, intraspinally (7 c. c.) spinal fluid K. McD.
July 10, intraspinally (5 c. c.) spinal fluid K. A. C.
September 18, intranasal application feces.

Rhesus No. 107.

1914. May 19, intraspinally (5 c. c.) spinal fluid J. W.
May 30, intraspinally (5 c. c.) spinal fluid L. W.
September 18, intranasal application feces.

Rhesus No. 108.

1914. May 19, intraspinally (5 c. c.) spinal fluid J. W.
May 30, intraspinally (5 c. c.) spinal fluid M. A.
September 19, intranasal application feces.
1915. June 21–23, intraperitoneally (60 c. c.) Berkefeld filtrate feces.

Rhesus No. 109.

1914. May 19, intraspinally (6 c. c.) spinal fluid R. B.
May 30, intraspinally (5 c. c.) spinal fluid M. A.
September 19, intranasal application feces.
1915. June 20–23, intraperitoneally (60 c. c.) Berkefeld filtrate feces.

Rhesus No. 110.

1914. June 12, intraspinally (8 c. c.) spinal fluid R. P.
July 10, intraspinally (5 c. c.) spinal fluid C. H.
September 19, intranasal application feces.

Rhesus No. 111.

1915. June 17–23, intraperitoneally (130 c. c.) Berkefeld filtrate feces.
Died September 18, 1915, cause of death not apparent at autopsy.

Rhesus No. 114.

1914. May 27, intraspinally (2 c. c.), intraperitoneally (2 c. c.) gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 19, intranasal application feces.
Died July 8, 1915; tuberculosis.

Rhesus No. 115.

1914. May 27, intraspinally (2 c. c.), intraperitoneally (2 c. c.) gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 18, intranasal application feces.

Rhesus No. 116.

1914. May 27, intraspinally (2 c. c.), intraperitoneally (2 c. c.) gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 18, intranasal application feces.

Rhesus No. 117.

1914. June 3, intracerebrally (1 c. c.), intramuscularly (1 c. c.) gauze filtrate, brain, spinal fluid, and membranes autopsy No. 9.
1914. September 18, intranasal application feces.

Rhesus No. 119.

1914. May 27, intracerebrally (1 c. c.), intramuscularly (1 c. c.), gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 18, intranasal application feces.
1915. June 17–20, intraperitoneally (70 c. c.) Berkefeld filtrate feces.
Died June 24, 1915; peritoneum everywhere apparently normal. Bile colored mucous membrane, stomach, and duodenum.

Rhesus No. 120.

1914. May 27, intracerebrally (1 c. c.), intraperitoneally (1 c. c.), gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 18, intranasal application feces.
1915. June 17–23, intraperitoneally (110 c. c.) Berkefeld filtrate feces.
Died June 30, 1915; intestines matted together; liver and intestines adherent to abdominal wall.

Rhesus No. 121.

1914. May 27, intraspinally (2 c. c.), intraperitoneally (2 c. c.), gauze filtrate, brain, spinal cord, and membrane autopsy No. 9.
September 19, intranasal application feces.

Rhesus No. 123.

1914. June 3, intracerebrally (1 c. c.), intraperitoneally (1 c. c.), gauze filtrate, brain, spinal cord, and membranes autopsy No. 9.
September 18, intranasal application feces.

HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp.-Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *bacillus pestis.* By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis.* By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyde and sulphur dioxid. By M. J. Rosenau.

†No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

†No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

*No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi.* By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestede genus *Hymenolepis;* by Ch. Wardell Stiles.

*No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

*No. 15. Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allen J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in *man*, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

*No. 19.—A method for inoculating animals with precise amounts. By M. J. Rosenau.

*No. 20.—A zoological investigation into the cause, transmission, and source of Rocky Mountain "spotted fever." By Ch. Wardell Stiles.

*No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Rosenau.

*No. 22.—Chloride of zinc as a deodorant, antiseptic, and germicide. By T. B. McClintic.

*No. 23.—Changes in the pharmacopœia of the United States of America, eighth decennial revision. By Reid Hunt and Murray Galt Motter.

No. 24.—The international code of zoological nomenclature as applied to medicine. By Ch. Wardell Stiles.

*No. 25.—Illustrated key to the cestode parasites of man. By Ch. Wardell Stiles.

*No. 26.—On the stability of the oxidases and their conduct toward various reagents. The conduct of phenolphthalein in the animal organism. A test for saccharin, and a simple method of distinguishing between cumarin and vanillin. The toxicity of ozone and other oxidizing agents to lipase. The influence of chemical constitution on the lipolytic hydrolysis of ethereal salts. By J. H. Kastle.

*No. 27.—The limitations of formaldehyde gas as a disinfectant with special reference to car sanitation. By Thomas B. McClintic.

*No. 28.—A statistical study of the prevalence of intestinal worms in man. By Ch. Wardell Stiles and Philip E. Garrison.

*No. 29.—A study of the cause of sudden death following the injection of horse serum. By M. J. Rosenau and John F. Anderson.

†No. 30.—I. Maternal transmission of immunity to diphtheria toxine. II. Maternal transmission of immunity to diphtheria toxine and hypersusceptibility to horse serum in the same animal. By John F. Anderson.

†No. 31.—Variations in the peroxidase activity of the blood in health and disease. By Joseph H. Kastle and Harold L. Amoss.

†No. 32.—A stomach lesion in guinea pigs caused by diphtheria toxine and its bearing upon experimental gastric ulcer. By M. J. Rosenau and John F. Anderson.

*No. 33.—Studies in experimental alcoholism. By Reid Hunt.

†No. 34.—I. *Agamofilaria georgiana* n. sp. an apparently new roundworm parasite from the ankle of a negress. II. The zoological characters of the roundworm genus *Filaria* Mueller, 1787. III. Three new American cases of infection of man with horsehair worms (species *Paragordius varius*), with summary of all cases reported to date. By Ch. Wardell Stiles.

†No. 35.—Report on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle. (Including articles contributed by Ch. Wardell Stiles, Joseph Goldberger, and A. M. Stimson.)

†No. 36.—Further studies upon hypersusceptibility and immunity. By M. J. Rosenau and John F. Anderson.

†No. 37.—Index-catalogue of medical and veterinary zoology. Subjects: Trematoda and trematode diseases. By Ch. Wardell Stiles and Albert Hassall.

No. 38.—The influence of antitoxin upon post-diphtheritic paralysis. By M. J. Rosenau and John F. Anderson.

†No. 39.—The antiseptic and germicidal properties of solutions of formaldehyde and their action upon toxines. By John F. Anderson.

†No. 40.—1. The occurrence of a proliferating cestode larva (*Sparganum proliferum*) in man in Florida, by Ch. Wardell Stiles. 2. A reexamination of the type specimen of *Filaria restiformis* Leidy, 1880=*Agramomermis restiformis*, by Ch. Wardell Stiles. 3. Observations on two new parasitic trematode worms: *Homalogaster philippinensis* n. sp., *Agamodistomum nanus* n. sp., by Ch. Wardell Stiles and Joseph Goldberger. 4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

†No. 41.—Milk and its relation to the public health. By various authors.

†No. 42.—The thermal death points of pathogenic microorganisms in milk. By M. J. Rosenau.

†No. 43.—The standardization of tentanus antitoxin (an American unit established under authority of the act of July 1, 1902). By M. J. Rosenau and John F. Anderson.

No. 44.—Report No. 2 on the origin and prevalence of typhoid fever in the District of Columbia, 1907. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle.

†No. 45.—Further studies upon anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 46.—*Hepatozoon perniciosum* (n. g., n. sp.); a hæmorgregarine pathogenic for white rats; with a description of the sexual cycle in the intermediate host, a mite (*lelaps echidnimus*). By W. W. Miller.

No. 47.—Studies on thyroid: I. The relation of iodine to the physiological activity of thyroid preparations. By Reid Hunt and Atherton Seidell.

No. 48.—The physiological standardization of digitalis. By Charles Wallis Edmunds and Worth Hale.

No. 49.—Digest of comments on the United States pharmacopœia. Eighth decennial revision for the period ending December 31, 1905. By Murray Galt Motter and Martin I. Wilbert.

No. 50.—Further studies upon the phenomenon of anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 51.—Chemical tests for blood. By Joseph H. Kastle.

No. 52.—Report No. 3 on the origin and prevalence of typhoid fever in the District of Columbia (1908). By M. J. Rosenau, Leslie L. Lundsen, and Joseph H. Kastle.

No. 53.—The influence of certain drugs upon the toxicity of acetanilide and antipyrine. By Worth Hale.

No. 54.—The fixing power of alkaloids on volatile acids and its application to the estimation of alkaloids with the aid of phenolphthalein or by the Volhard method. By Elias Elvove.

No. 55.—Quantitative pharmacological studies; adrenalin and adrenalinlike bodies. By W. H. Schultz.

No. 56.—Milk and its relation to the public health. (Revised edition of Bulletin No. 41.) By various authors.

No. 57.—I. The presence of tubercle bacilli in the circulating blood in clinical and experimental tuberculosis. By John F. Anderson. II. The viability of the tubercle bacillus. By M. J. Rosenau.

No. 58.—Digest of comments on the pharmacopœia of the United States of America (eighth decennial revision) and the national formulary for the period ending December 31, 1906. By Murray Galt Motter and Martin I. Wilbert.

No. 59.—The oxidases and other oxygen catalysts concerned is biological oxidations. By Joseph Hoeing Kastle.

No. 60.—A study of the anatomy of Watsonius (n. g.), Watsoni of man, and of 19 allied species of mammalian trematode worms of the superfamily *Paramphistomoidea*. By Ch. Wardell Stiles and Charles Goldberger.

No. 61.—Quantitative pharmacological studies; Relative physiological activity of some commercial solutions of epinephrin. By W. H. Schultz.

No. 62.—The taxonomic value of the miscropic structure of the stigmal plates in the tick genus Dermacentor. By Ch. Wardell Stiles.

† No. 63.—Digest of comments on the pharmacopœia of the United States of American (eighth decennial revision) and on the national formulary (third edition) for the calendar year ending December 31, 1907. By Murray Galt Motter and Martin I. Wilbert.

No. 64.—Studies upon anaphylaxis with special reference to the antibodies concerned. By John F. Anderson and W. H. Frost.

No. 65.—Facts and problems of rabies. By A. M. Stimpson.

No. 66.—I. The influence of age and temperature on the potency of diphtheria antitoxin. By John F. Anderson. II. An organism (*Pseudomonas protea*) isolated from water, agglutinated by the serum of typhoid-fever patients. By W. H, Frost. III. Some considerations on colorimetry, and a new colorimeter. By Norman Roberts. IV. A gas generator in four forms, for laboratory and technical use. By Norman Roberts.

† No. 67.—The solubilities of the pharmacopœial organic acids and their salts. By Atherton Seidell.

No. 68.—The bleaching of flour and the effect of nitrites on certain medicinal substances. By Worth Hale.

No. 69.—The effects of restricted diet and of various diets upon the resistance of animals to certain poisons. By Reid Hunt.

No. 70.—A study of melting point determinations with special reference to the melting point requirements of the United States pharmacopœia. By George A. Menge.

No. 71.—1. Some known and three new endoparasitic trematodes from American fresh-water fish. By Joseph Goldberger. 2. On some new parasitic trematode worms of the genus *Telorchis*. By Joseph Goldberger. 3. A new species of *Athesmia* from a monkey. By Joseph Goldberger and Charles G. Crane.

† No. 72.—I. Report on an outbreak of typhoid fever at Omaha, Nebr. (1909–1910), by L. L. Lumsden. II. The water supply of Williamson, W. Va., and its relation to an epidemic of typhoid fever. By W. H. Frost.

No. 73.—The effect of a number of derivatives of choline and analoguos compounds on the blood pressure. By Reid Hunt and R. de M. Taveau.

No. 74.—Digitalis standardization and the variability of crude and of medicinal preparations. By Worth Hale.

No. 75.—Digest of comments on the pharmacopœia of the United States of America (eighth decennial revision) and the national formulary (third edition) for the calendar year ending December 31, 1908. By Murray Galt Motter and Martin I. Wilbert.

No. 76.—The physiological standardization of ergot. By Charles Wallis Edmunds and Worth Hale.

No. 77.—Sewage pollution of interstate and international waters with special reference to the spread of typhoid fever. By Allan J. McLaughlin.

No. 78.—Report No. 4 on the origin and prevalence of typhoid fever in the District of Columbia (1909). By L. L. Lumsden and John F. Anderson. (Including articles contributed by Thomas B. McClintic and Wade H. Frost.)

No. 79.—Digest of comments on the pharmacopœia of the United States of America (eighth decennial revision) and the national formulary (third edition) for the calendar year ending December 31, 1909. By Murray Galt Motter and Martin I. Wilbert.

No. 80.—Physiological studies in anaphylaxis. Reaction of smooth muscle from various organs of different animals to proteins. (Including reaction of muscle from nonsensitized, sensitized, tolerant, and immunized guinea pigs.) By William H. Schultz.

No. 81.—Tissue proliferation in plasma medium. By John Sundwall.

No. 82.—I. Method of standardizing disinfectants with and without organic matter. By John F. Anderson and Thomas B. McClintic. II. The determination of the phenol coefficient of some commercial disinfectants. By Thomas B. McClintic.

No. 83.—I. Sewage pollution of interstate and international waters with special reference to the spread of typhoid fever. II. Lake Superior and St. Marys River. III. Lake Michigan and the Straits of Mackinac. IV. Lake Huron, St. Clair River, Lake St. Clair, and the Detroit River. V. Lake Ontario and St. Lawrence River. By Allan J. McLaughlin.

No. 84.—Digest of comments on the pharmacopœia of the United States of America (eighth decennial revision) and on the national formulary (third edition) for the calendar year ending December 31, 1910. By Murry Galt Motter and Martin I. Wilbert.

No. 85.—Index catalogue of medical and veterinary zoology. Subjects: Cestoda and cestodaria. By Ch. Wardell Stiles and Albert Hassall.

No. 86.—Studies on typhus. By John F. Anderson and Joseph Goldberger.

No. 87.—Digest of comments on the pharmacopœia of the United States of America (eighth decinnial revision) and on the national formulary (third edition) for the calendar year ending December 31, 1911. By Murray Galt Motter and Martin I. Wilbert.

No. 88.—Method for determining the toxicity of coal-tar disinfectants, together with a report on the relative toxicity of some commercial disinfectants. By Worth Hale.

No. 89.—Sewage pollution of interstate and international waters with special reference to the spread of typhoid fever. VI. The Missouri River from Sioux City to its mouth. By Allan J. McLaughlin.

No. 90.—Epidemiologic studies of acute anterior poliomyelitis. I. Poliomyelitis in Iowa, 1910. II. Poliomyelitis in Cincinnati, Ohio, 1911. III. Poliomyelitis in Buffalo and Batavia, N. Y., 1912. By Wade H. Frost.

No. 91—I. The cause of death from subdural injections of serum. By Worth Hale. II. Some new cholera selective media. By Joseph Goldgerger.

No. 92.—Gaseous impurities in the air of railway tunnels. By Atherton Seidell and Philip W. Meserve.

No. 93.—Digest of comments on the pharmacopœia of the United States of America (eighth decinnial revision) and on the national formulary (third edition) for the calendar year ending December 31, 1912. By Murray Galt Motter and Martin I. Wilbert.

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